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Editorial

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CUSHING'S SYNDROME—PITUITARY OR ADRENAL ORIGIN?*

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AS METHODS for the estimation of corticosteroids in blood and urine have become increasingly accurate and reproducible, the etiology of adrenal hyperfunction has received increased attention. Biochemical studies have demonstrated the enzymatic defects present in children with congenital adrenal hyperplasia. An enzymatic deficiency in these patients, resulting in deficient hydrocortisone secretion, stimulates excess ACTH elaboration and a marked increase in androgen production. No such defect has been found, however, in patients who suffer from adrenal hyperactivity of the type originally described by Cushing. Although Cushing was impressed by the pituitary changes noted in some of his patients and felt that the etiology of the adrenal hyperfunction was, in most cases, due to an abnormality of the anterior pituitary,[2] modern workers have not demonstrated as significant a correlation between Cushing's syndrome and pituitary disease. Some patients have been demonstrated to have pituitary tumors in association with this syndrome, and in these cases the pituitary etiology seems likely,[3] although methods for the measurement of ACTH have not been sufficiently sensitive to demonstrate an increased ACTH production in such patients.

At this time it seems probable that Cushing's syndrome may result from multiple causes, all of which ultimately present in the same characteristic manner produced by increased amounts of corticosteroids of the hydrocortisone type. These various types may be conveniently divided into bilateral hyperplasia, benign adenoma, carcinoma, and pituitary tumor.

*The term Cushing's *syndrome* will be used in this discussion to refer to the well-accepted clinical picture regardless of etiology.[1]

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BENIGN ADENOMAS OF THE ADRENAL CORTEX

Benign adenomas of the adrenal cortex may be divided into autonomous and nonautonomous tissue. It is not uncommon at autopsy, particularly in patients with hypertension, to find multiple adenomas in the adrenal cortex. These, however, may be separated from the adenomas which produce Cushing's syndrome. Adenomas which result in Cushing's syndrome are generally single in nature, and produce sufficient corticosteroid to suppress the production of normal quantities of pituitary ACTH, and thus cause atrophy of surrounding adrenal tissue and of the contralateral gland. These single adenomas generally do not respond to ACTH, nor are they suppressed following corticosteroid administration. Examination of urinary corticosteroids usually demonstrates a marked increase in compounds of the 17-hydroxycorticosteroid type and less commonly an increase in 17-ketosteroids (aldosterone- or androgen-producing adenomas of the adrenal cortex would, of course, not follow these rules). It must be remembered that no single test, such as response to ACTH or suppression by exogenous corticoids, has consistently served as an absolute differential between adenoma and hyperplasia,[4] but the general findings, as noted above, appear to apply in the majority of cases.

HYPERPLASIA OF THE ADRENAL CORTICES

Hyperplasia of the adrenal cortices, in contradistinction to the adenomas mentioned above, affects both adrenal glands. Associated with this is an increase in 17-hydroxycorticosteroids, 17-ketosteroids, and, in some cases, aldosterone in the urine of these patients. There is usually a hyperactive response to ACTH as shown by a greater than normal increment in urinary 17-hydroxycorticosteroids and 17-ketosteroids over base line following the administration of a given amount of ACTH. For the ACTH test the intravenous route is definitely preferable.[5] Results obtained with intramuscular ACTH can be considered only if the response is positive in nature and the possibility must always be kept in mind that insufficient ACTH, to produce the maximum stimulation required for proper diagnosis, reached the adrenal cortex. Most patients with Cushing's syndrome have a decrease in secretion from the adrenal following the administration of large quantities of corticosteroids. Liddle has recently suggested that a proper differential may be made by the daily administration of 2 mg. of dexamethosone (Decadron) (0.5 mg. every 6 hours) for 2 days, which will suppress the adrenals in all normal subjects but will not suppress the adrenal activity of patients with Cushing's syndrome, and the daily administration of 8 mg. of dexamethosone (2 mg. every 6 hours) for 2 days which will suppress the adrenals of patients with hyperplasia of the adrenal cortex.[6] Other investigators have not had as much success as has Liddle with an absolute differential between these cases, but it must be stated that the particular dose ranges recommended by Liddle have not been used. It should be noted that the patient with adrenal hyperplasia may have a nodular-appearing adrenal cortex, but will not have atrophy of surrounding adrenal tissue as noted for the single functioning adenoma referred to above.

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CARCINOMA OF THE ADRENAL CORTEX

Carcinomas of the adrenal cortex may be of more than one type physiologically and thus may produce a typical picture of Cushing's syndrome or may be strictly virilizing in type and produce essentially androgens without any increase or, in some cases, an actual decrease in hydrocortisone secretion. They also may be mixed, producing any combination, amount, and proportion of hydrocortisone, androgen, and aldosterone. These tumors usually do not respond significantly to ACTH administration, but may show a relatively small increase in terms of total quantity of corticoids produced. Adrenal secretion in these tumors is not dependent on production of pituitary ACTH, and is not suppressed significantly by the administration of corticosteroids in the so-called "suppression test." In a few cases in which hypophysectomy has been carried out, there has been no lasting effect on steroid secretion, although there may be a temporary reduction following removal of the pituitary gland. There may be contralateral atrophy of adrenal cortical tissue in the presence of a carcinoma as there is in the presence of a benign functioning adenoma. Metastases frequently occur.

PITUITARY TUMORS

The association of demonstrable tumors of the pituitary gland with Cushing's syndrome is generally not considered to occur in more than 5 to 10 per cent of patients with this condition but, as previously noted, the possiblity that small tumors are present is usually impossible to rule out. Patients with obvious tumors of the pituitary gland and adrenal hyperfunction present the picture seen in hyperplasia with increase in 17-hydroxycorticosteroids and 17-ketosteroids in the urine. In a few cases attempts have been made to measure plasma ACTH; although it has generally not been possible to demonstrate an elevation of this pituitary hormone, it should be remembered that the techniques which have been employed are not of great enough sensitivity to estimate ACTH in the plasma of normal subjects. There might be, therefore, a moderate elevation over normal which the assay technique would not demonstrate. It is worth noting that the author has recently been able to demonstrate significantly increased levels of ACTH in 2 patients who have Cushing's syndrome and Liddle[6] has reported a similar case. All 3 patients had had partial adrenalectomies prior to the time at which the plasma was obtained for ACTH determination, and had elevated levels of 17-hydroxycorticosteroids in the urine at the time of sampling. These data indicate that at least some patients with Cushing's syndrome will have rather markedly elevated levels of ACTH in the peripheral blood.

PITUITARY TUMORS OCCURRING FOLLOWING ADRENALECTOMY FOR CUSHING'S SYNDROME

A syndrome which is characterized by hyperpigmentation, tumors of the pituitary, and markedly increased levels of plasma ACTH has recently been noted in a number of patients following bilateral adrenalectomy for Cushing's syndrome.[7-9] A return of ACTH in the plasma to more nearly normal levels and marked loss of pigmentation following hypophysectomy or sufficient irradiation

to the pituitary gland demonstrates the pituitary etiology of this syndrome. In no case was an attempt made to measure ACTH in the plasma prior to the adrenalectomy, and thus it is not possible to say with certainty that there was not an elevation of ACTH with the original occurrence of Cushing's syndrome. In none of these cases was a tumor of the pituitary gland observed radiologically or evidence for it noted clinically prior to the adrenalectomy. The question has thus been raised as to whether these tumors represent continued growth of small unidentified tumors which were the original inciting factor of the Cushing's syndrome or whether removal of the adrenal glands has resulted in an abnormal stimulus which has induced growth of the pituitary tumor. The latter case would be analogous to other pituitary tumors which have been noted following suppression of thyroid and gonadal function in animal experimentation.[10,11] Although at the present time it is not possible to establish definitely whether these tumors represent new growth or continued growth, it would appear likely, as the patients have all had Cushing's syndrome prior to the appearance of the pituitary tumor, that there was increased ACTH production before evidence of the tumor appeared. The ultimate etiological agent is still not known, nor is the extent to which stimulus to growth of the pituitary tumor has been brought about by adrenalectomy.

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SUMMARY

It seems probable that the etiology of Cushing's syndrome can be conveniently divided into at least two categories and perhaps more. First, there are patients who have a condition limited to the adrenal gland, such as the benign adenomas and carcinomas, which generally do not appear to be dependent upon pituitary ACTH production. There is no primary defect in pituitary secretion in these patients and the reason for the adrenal disturbance is unknown. Second, there is a group of patients in whom tumors of the pituitary gland are associated with Cushing's syndrome. In most of these the direct determination of increased levels of plasma ACTH has not been carried out, but the connection seems probable and is strengthened by the recent demonstration of elevated plasma ACTH in a few of these patients. Third, there is a group of patients who may or may not fall into the group with primary pituitary disease. These are patients who have hyperplasia of both adrenal cortices in whom there is fairly good evidence that there is increased production of ACTH producing adrenal hypertrophy, but in whom there has been no demonstration of clear-cut pituitary pathology. The fact that one can suppress adrenal function in these patients, if sufficient corticosteroid is administered, suggests that normal pituitary controls are not abolished, but seems to indicate that the "thermostat" has been set up in such a way that the anterior pituitary secretes ACTH to produce a higher than normal level of corticosteroid production. It is possible that the pathology of Cushing's syndrome is in neither the adrenal nor the pituitary gland in cases with bilateral hyperplasia. A "relative deficiency" in other tissues might result in a stimulus to increase ACTH just as it does in conditions of stress. Thus it has been demonstrated that following trauma to dogs, plasma levels of ACTH and of corticosteroids may be simultaneously elevated.[12] It is not possible at this

time to state definitely whether pituitary tumors, which occur following bilateral adrenalectomy for Cushing's syndrome, occur as the result of continued growth of small tumors or may possibly be the result of a stimulus of peripheral origin which acts to stimulate ACTH secretion. A combination of such a stimulus to the formation of Cushing's syndrome and removal of both adrenal glands with resultant fall in plasma corticosteroid levels may act as a powerful stimulus to ACTH secretion and be followed by tumor formation in the anterior pituitary gland.

Further knowledge will have to be obtained along a number of lines of investigation before we have a clear understanding of the factors which produce Cushing's syndrome. Specifically, a better understanding must be obtained of the relationships between the pituitary production of ACTH and the stimulus to this production, and better means must be developed for the determination of ACTH in blood.

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EPIDEMIOLOGY AND PATHOLOGY OF CORONARY ARTERY DISEASE: I. METHOD OF STUDY

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THE contribution that epidemiology might make to knowledge regarding coronary heart disease was the subject of a series of discussions held several years ago under the auspices of the New York State Department of Health. Clinicians emphasized the diagnostic sensitivity of the electrocardiogram, while at the same time they recalled the atheromatous lesions not detectable clinically, but frequently found in the coronary arteries post mortem. Laboratory representatives reviewed the many suggestive findings yielded by their studies, emphasizing associations between blood lipids and coronary heart disease, and describing the lesions produced experimentally in animals which, though resembling human atherosclerosis, were only occasionally accompanied by infarction in the myocardium.[1*] Participants from public health fields elaborated on the recent strikingly high death rates, and their variation with such demographic characteristics as age, sex, race, geographic region, and socioeconomic status.

From ensuing discussions of the possible additions to existing knowledge which might be gained from an epidemiologic study of coronary heart disease, particularly one seeking factors of etiological significance, three points appeared most salient: (1) assuming that death certificates were not enormously inaccurate, the disease was most certainly very frequent and highly fatal, particularly among middle-aged and elderly males; (2) although the clinician was able to recognize

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*Since 1954, when these matters were under consideration, two groups of investigators have succeeded in producing myocardial infarcts in animals: (1) Myasnikov, employing cholesterol feeding and physical stress,[2] and (2) Thomas and Hartroft using high fat diets plus chemical additives.[3]

the disease when myocardial damage was present, atherosclerosis in the coronary arteries usually escaped his detection; and (3) the complete disease process had not been satisfactorily reproduced in animals.

Considering this set of circumstances, the group reached several tentative conclusions. First, an epidemiologic study appeared justified, since (a) the disease was of high incidence and thus warranted a population approach, and (b) a study of its ecology, the primary concern of epidemiologists, might reveal that it was associated with certain characteristics or activities in a manner suggesting a causal relationship.

Second, an approach appeared promising in which attention would be directed toward coronary artery atherosclerosis in its varying degrees of severity in relation to degree of exposure to epidemiologic variables, an approach that would require cooperative study by the pathologist and the epidemiologist. This method would have the major advantage of bringing a large portion of the spectrum of the disease under study, presumably ranging from little or no involvement of the coronary arteries to severe arterial disease and myocardial complications. Such an approach would necessarily be based upon the assumption that coronary artery atherosclerosis plays a major part in the etiology of coronary heart disease. Data from this study bearing upon this assumption are presented in a later section.

A study design that would bring into focus the full range of gradations of atherosclerosis would make it possible to identify individuals in whom the disease was clearly absent. According to the evidence of necropsy studies,[4,5] individuals without atherosclerosis* are generally believed to constitute a small minority among middle-aged and elderly males. If such "noncase" individuals were identified and utilized as a control group, presumably they would contrast more sharply with severe "cases" in terms of etiological factors than would a clinically selected "noncase" group in which a large proportion of individuals with diseased arteries would necessarily be included. In this design, the "case" group would be composed of individuals with gradations of coronary artery atherosclerosis from subclinical stages to clinically manifest disease. "Noncases" have been particularly elusive as subjects for study in that they are not only apparently relatively rare among older males, but are also not clearly identifiable clinically. It appeared especially desirable, therefore, to identify these "noncases" with precision so that differences between cases and controls, in epidemiologic attributes, would stand out more sharply. It seems likely that difficulties in identifying true disease-free "control" individuals have hampered many clinical investigations into the etiology of coronary heart disease. If atherosclerosis of the coronary arteries is a major process underlying coronary heart disease, the inability to identify precisely the "noncase" may account for some of the difficulty in finding striking differences between "cases" and "controls" in regard, for example, to smoking habits or dietary patterns. This seems disadvantageous whether the approach be retrospective or prospective.

*The term "without," in this context, has a relative meaning, not distinguishable practically from "little" atherosclerosis, since this difference is likely to be a function of the extensiveness of the examination.

Thus, it appeared desirable to avoid this disadvantage in the design of an epidemiologic study, particularly as it was not anticipated that causal factors would be found very readily. If they were, pathologists and clinicians would, of course, have identified them long ago. The problem, therefore, seemed to invite a study approach which might prove rewarding by virtue of its attention to preclinical aspects of the disease.

On the basis of these considerations, efforts were directed toward designing an epidemiologic study which would both encompass the total range of atherosclerosis in the coronary arteries and differentiate among degrees of severity of the disease within this range, without, of course, neglecting myocardial disease per se. Since the necessary information about atherosclerosis could be supplied only by postmortem examination, such a study would necessarily be restricted to a population of autopsied patients. Although the study could be designed to include a series of consecutive autopsies following death from any cause, two serious limitations would remain. First, the study population would be a selected group, not representative of the general population: individuals who died in a hospital, and, among these, individuals whose relatives consented to an autopsy. Second, it would be necessary to collect epidemiologic data under circumstances that would not represent a very satisfactory interview situation: questioning erminally ill patients and/or their close relatives.

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However, in spite of these limitations, certain important advantages were apparent. First, as mentioned earlier, "noncases" could be identified with certainty. Second, gradations of the disease process could be measured at necropsy which should reflect, to a reasonable degree, levels of the complex process of atherosclerosis. These measurements could then be related to degree of exposure to each of the epidemiologic variables under study. Thus, a more informative examination of relationships would be possible than in previous studies limited in their analyses to a "case" vs. "control" dichotomy. For example, it could be seen if amount of disease varied consistently with amount of exposure. Third, identification of preclinical levels of atherosclerosis would make it possible to discover associations between preclinical disease specifically, and epidemiologic factors, which, in turn, could lead to highly desirable preventive action, the latter directed at levels of atherosclerosis that precede clinical illness by a generous margin.

For these reasons, a pathologic-epidemiologic study was inaugurated. Its design and operation are described in subsequent sections of the present report. Preliminary data pertaining to a relationship basic to this approach, that between atherosclerosis and infarction, are also presented and briefly discussed.

DESIGN

With generous assistance from associates in epidemiology, pathology, cardiology, and statistics in the New York State Department of Health and the Albany Medical College, a plan of investigation was developed, and, in March of 1955, a pilot study was inaugurated. Since that time the approach has been expanded to include additional types of data, and certain improvements in

methodology have been instituted. The assumptions and other details of the design are described below together with procedures that are now in operation.

Basic Assumptions.—Two theoretical assumptions underlie this approach to the study of coronary heart disease: first, that coronary artery atherosclerosis is closely related to, and usually precedes, ischemia and infarction of the myocardium. The term atherosclerosis is broadly defined to include lipoid, fibrous, and calcified plaques, as well as any major part the process may play, functionally, in thrombus formation, either as a stage resulting from an organized clot, or in the precipitation of a thrombus. Second, it is assumed that, in addition to possible genetic factors, the development of atherosclerosis proceeds in association with, if it is not, in fact, caused by, patterns of activity, exposure, or behavior as yet unknown or not clearly identified.

In terms of the data required by this approach to coronary heart disease, several methodologic assumptions are also necessary: (1) that the frequency and intensity of an individual's exposure to the epidemiologic variables (i.e., life-style patterns) under investigation are known to the individual and to his close family associates to an extent sufficient to permit valid classification if relatively broad categories are employed; (2) that reasonably valid data regarding these variables or patterns may be obtained from verbal responses to interview questions; and thus (3) that a study of a series of consecutively autopsied patients may be uniquely informative, despite the limitations discussed earlier, by permitting the direct comparison of pathologic data with interview data regarding these "life-style" patterns.

Objective.—The chief objective of the study is to examine relationships between the precise state of health of the coronary arteries and selected epidemiologic and clinical variables. The pathologic data provide a description of the degree of atherosclerosis (including its absence) found in the coronary arteries, as well as the condition of the myocardium. The epidemiologic and clinical data are concerned with, for example, residence, occupation, and smoking histories, alcohol consumption, and selected diseases and chronic conditions.

Many relationships are under analysis, some examples of which are:

1. Is a greater degree of coronary artery atherosclerosis as manifested, for example, by artery wall thickness, associated with:
   a. A predominantly urban history of residence, as compared with a predominantly rural history?
   b. A history of sedentary occupations suggesting little physical activity, as compared with occupations suggesting more activity among males?
   c. Certain patterns arising from combinations of variables as, for example, heavy compared with light occupations among urban and rural males?
   d. Single variables considered with additional degrees of refinement such as an occupational history suggesting a shift from heavy to light physical activity, as compared with a history of heavy or light occupations throughout life?

2. Is the presence of infarction or thrombosis, as detected in postmortem examination, associated with the types of the epidemiologic patterns described above?

These examples illustrate the primary objective: to explore as fully as possible relationships between the pathologic and epidemiologic data, and to examine any associations found from all possible vantage points. In addition, relationships within each set of data are being examined, e.g., does the extent of atherosclerosis vary directly with the frequency of infarction?

How profitably such questions can be explored is ultimately dependent upon: (a) the validity of both interview and pathology methods, and (b) the degree of confidence with which inferences can be drawn from a study population of hospital patients who come to autopsy.

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METHODS

Pathology.—A cooperative plan of study was drawn up in consultation with the chairman of the Department of Pathology of the Albany Medical College, Dr. Arthur W. Wright.* The capabilities of the professional staff and the facilities of this institution adequately met the needs of the study. The Department is accredited for training pathologists for Board certification. Consent for autopsy is requested for all deaths occurring in the adjoining Albany Hospital and, during recent years, such consent has been obtained for 60 to 65 per cent of the 600 to 700 deaths that occur annually. The Albany Hospital is a general hospital of 635 beds which serves the area in and around Albany, New York, drawing some patients from areas adjacent to Albany County as well.

The procedures followed by the Department in performing autopsies and recording findings are similar, with minor variations, to those employed in many teaching institutions. Each autopsy is assigned to a member of the resident staff, who, under the supervision of a senior staff member, carries out a prescribed series of gross and microscopic examinations, which are modified, as appropriate, at sites of disease or suspected disease. Examinations are thus generally similar from case to case unless, as happens on occasion, the consent for autopsy specifically limits the exploration. Following consultation with the supervising staff member and approval of the chairman, all findings are recorded in a case protocol.

When specific plans for the study were considered, however, it appeared that the description of the coronary arteries, as stated in the protocol, would not lend itself to translation into quantitative terms. Certain qualitative expressions, such as "calcification," might have been selected, which would probably have been indicative of severe atherosclerosis. Morris[6] employed this indicator, together with other descriptive terms, in a review of autopsy records at the London Hospital. However, a method for the quantitation of both the extent and severity of the disease process seemed preferable, and it also appeared desirable to employ highly consistent procedures which would yield results stated in immediately comparable terms. Indeed, this need for objectivity and comparability was stressed recently by the Study Group on the Classification of Atherosclerotic

*Dr. Wright retired from this position on July 1, 1959, and Dr. Wilbur A. Thomas was appointed chairman of the Department of Pathology.

Lesions, of the World Health Organization.[7] Further, it appeared necessary that the procedures be carried out under the close supervision of one responsible individual, in order that maximum uniformity and continuity might be achieved in the collection of data. One of the authors (A. D.), a senior staff member of the Department of Pathology, assumed this responsibility. A set of procedures was adopted which has been followed, with modifications as noted, up to the present time. These procedures may be summarized as follows:

1. All patients on whom autopsies were performed, aged 15 and older, are included in the study population, regardless of the cause of death.

2. A special examination of the major coronary arteries is made. During the first 2½ years of data collection, this examination consisted of: (a) making a series of cross-sectional cuts, at approximately 0.5 cm. intervals, along the course of each artery, (b) inspecting, in the gross, each cut surface, (c) making caliper measurements of internal and external diameters at selected sites where thickening of the vessel wall was detected (each site being chosen to characterize the thickness of that portion of the vessel wall), and (d) noting areas as "thin wall" where no thickening was visible and estimating the proportion of the total vessel length with no thickening. These findings were entered on a diagrammatic chart (Fig. 1). From this record of the coronary artery examination, several different quantitative expressions of atherosclerosis in the coronary arteries (singly and in combination) were calculated.

Other measurement procedures have been explored: (a) determining internal and external vessel diameters under a dissecting microscope, (b) from camera lucida projections of vessel cross-sections, tracing internal and external wall circumferences with determination of wall and lumen areas by planimetry, and (c) determining volume of removed coronary arteries by measuring liquid displaced.

3. Additional related findings in the heart (e.g., infarction, thrombosis, and calcification) are included in the study record.

4. Final anatomic diagnoses from the autopsy protocol are also included.

A series of methodologic studies has been made of the reliability of the various coronary artery measurement procedures. Details of these, together with descriptions of other special procedures in pathology, are presented in a report now in preparation.

Epidemiology.—An interview schedule was designed with the assistance of staff members of the Department of Health. Questions were formulated regarding a number of matters considered to be of possible significance in the etiology of coronary heart disease. These were as follows:

1. Patient's history with respect to:
   a. Residence and occupation, including physical activity.
   b. Smoking and drinking.
   c. Body weight.
   d. Various forms of heart disease and other selected diseases (e.g., hypertension, diabetes mellitus, peptic ulcer).
   e. Selected minor chronic conditions (e.g., chronic cough, diarrhea, headache) that may indicate stress.

2. Patient's usual consumption of ten commonly eaten foods high in fat content.
3. Cause of death or present health status of parents, siblings, and children of the patient.
4. Selected behavior patterns which, if usual or frequent, might reflect chronic emotional stress in the patient.

CORONARY ARTERY ATHEROSCLEROSIS WORK SHEET

FIXED ✓
FRESH _____

Autopsy No. A56-237
Date of autopsy 9/17/56

Name John Doe Age 47 Sex M Race W

Calcification: blue
Thrombus: red

If no calification check here ✓

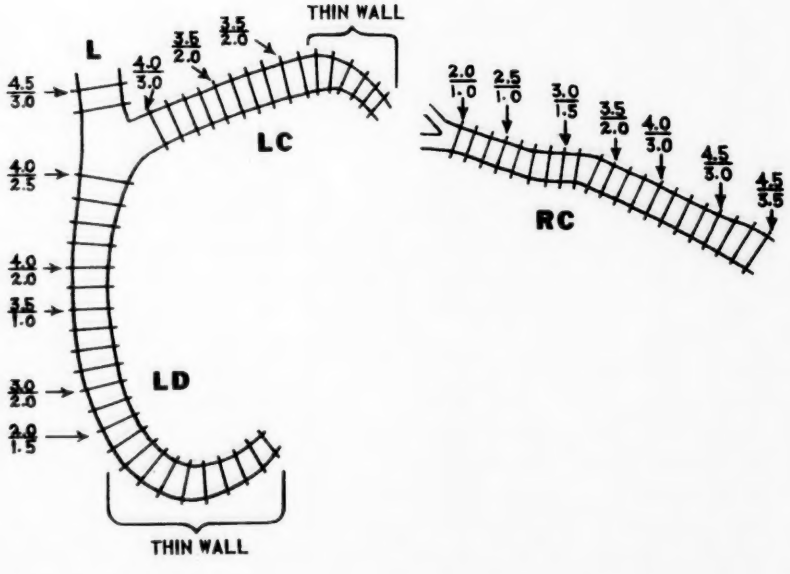

Fig. 1.—Example of completed diagrammatic chart with recordings of: (1) diameter measurements in millimeters, or (2) notation of "thin wall." Entries are made according to their approximate location. External diameters are entered above internal diameters.

$$\text{Thus: } \frac{2.0}{1.5} = \frac{\text{external diameter (mm.)}}{\text{internal diameter (mm.)}}$$

Coronary arteries are identified as follows: *L*, left coronary artery; *LD*, left descending branch; *LC*, left circumflex branch; *RC*, right coronary artery.

Interviews were first attempted with hospital patients who were not expected to survive the immediate episode of illness. As anticipated, a number of these interviews were judged to be quite unsatisfactory. For many patients, the subject matter of the interview was too far removed from the context of their critical condition to permit the carefully considered responses necessary. Instead, close family associates who were visiting them proved to be considerably more useful. Close relatives, of course, have long been utilized in taking medical histories under such circumstances as when a patient is not mentally clear. With regard to highly subjective matters, for example, the location and description of symptoms, the statements of relatives are often inaccurate. However, the extent to which close relatives were found to be sufficiently informed to supply reasonably accurate information in the areas of interest to this study was impressive enough to persuade us to direct the interview exclusively toward the available relative judged to be best informed, rather than toward the patient himself.

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This substitution made it possible to postpone the interview until after death, with the advantages of: (1) avoiding sizable "losses" in the population interviewed (only about 20 per cent of those interviewed during a critical illness could be expected to reach autopsy, largely because of the difficulty in predetermining death), and (2) conducting the interview at a time when the relative was less preoccupied and anxious than during the terminal illness of the patient. The immediate period of bereavement was avoided by delaying the interview until at least one month after the patient's death.

The usefulness of a relative as an informant was regarded as a matter subject at least to crude measurement. The degree of correspondence between an individual's statements about himself and statements made about him by his spouse was assessed in two special series of patient-spouse interviews conducted among hospital patients who were not acutely ill. Patient and spouse were interviewed simultaneously in separate rooms. In brief, it was found that the frequency of gross agreement varied both by subject area and by type of detail required within each area. As anticipated, the proportion of agreement was higher among responses to relatively gross questions regarding the presence or absence of a characteristic than among responses to questions concerned with degree, amount, or frequency. These methodologic studies have provided the basis for revisions of the interview schedule. Additional subject areas will be investigated similarly. Recently, certain aspects of the situation in which a relative serves as proxy respondent for a deceased person have also been explored by others with encouraging results.[8,9]

Following the early explorations, procedures were developed for interviewing relatives of autopsied patients. The main steps have been as follows:

1. Consultation with attending physician: When notification of autopsy is received, a junior staff member of the Department of Medicine contacts the physician who attended the patient during his terminal illness. After the study has been outlined, his suggestions are sought with regard to the relative who, in his opinion, will serve as the best informant. The response of these physicians has been, without exception, helpful and cooperative. From 1955 through 1958,

consent for the interview was withheld in 5 cases, or 0.4 per cent of the study population. In each instance this was owing to some special circumstance, such as legal considerations.

2. *Interview with relative of patient:* After an interval of one to several months following death, the interview assignment is given to one of the medical students employed and trained for this work. The student is given identifying information about the relative and the patient, together with the primary *clinical* diagnosis. The latter is furnished on the assumption that the student might appear to be poorly informed without this information, and that the relative will, in most instances, already have some knowledge regarding the major clinical findings. The interviewer, however, is not given the pathology findings in order that the interview may be conducted "blind" insofar as the condition of the coronary arteries and myocardium is concerned (i.e., to avoid any possible interview bias from such knowledge).

Interviews are usually scheduled in advance by telephone and conducted at the home of the relative. They have proceeded without incident in the majority of cases. Respondents are usually not only willing to cooperate, but often appear anxious to aid in "medical research". If the relative first assigned cannot be traced, has moved out of the area, refuses consent for the interview, or appears to be unreliable or uninformed, a second relative is sought, and then, if necessary, a third, and so on. Among autopsied patients having a relative from whom an interview was requested the proportion of refusals has been approximately 2 per cent per year.

Clinical.—Certain clinical findings obtainable from pre-existing records appeared to be useful supplements to the pathology and epidemiology data:

1. *Abstract of hospital record:* The records of all hospitalizations at Albany Hospital for each patient in the study are reviewed and systematically abstracted to include: diagnoses, electrocardiographic and chest x-ray findings, body weight, blood pressure, blood chemistry determinations, and specified aspects of previous illnesses considered relevant to coronary heart disease. This work was initially done by a junior staff member of the Department of Medicine, but the development of a detailed abstract form now permits the employment of fourth-year medical students for this work. The data available in the hospital record vary, of course, with the work-up, according to suspected diagnoses and length of hospitalization prior to death.

2. *Interview with family physician:* Recently, an effort has been initiated to identify long-term family physicians of each patient in order to obtain clinical data pertaining to earlier periods of his life. Interviews are directed chiefly toward manifestations of coronary heart disease, including any electrocardiographic findings; diagnoses of certain presumably related diseases; long-term, severe dietary or physical activity restriction; and all available height, weight, and blood pressure determinations, together with their dates.

Future Refinement of Methods.—Although progress has been made in developing reliable methods, further explorations are needed. In pathology these include, for example: (1) the continuation of attempts to achieve highly reproducible and objective techniques for artery wall measurement, and (2) the determination of the effects of muscular contraction and formalin fixation on the

dimensions of artery walls. In epidemiology, systematic analyses appear necessary in several areas, some of which are under way: (1) the "best" time interval after death to interview the patient's relative, "best" implying a compromise among intervals found most rewarding for each of several objectives, such as achieving maximum detail of recall, and avoiding the most acute period of bereavement shock; (2) the discovery of any systematic biases in responses to questions attributable to (a) the "halo effect" of death (or its reverse), and (b) relationships between the intelligence of a relative and his accuracy of recall, ability to answer the questions asked, and willingness to report; and (3) the relative merits of interviewers with and without medical training.

Follow-up.—During the 4-year period, 1955 to 1959, data were collected relating to 1,296 necropsies in which the coronary arteries were studied.* The pathology procedures included, in addition, a special examination of the myocardium during the latter part of this period. Hospital records were abstracted and relatives were routinely interviewed until July, 1959, when these steps were temporarily discontinued pending revision of the interview schedule and modifications in the pathology procedures.

Interviews with relatives have been completed for 81 per cent of 1,296 necropsies studied. Since a relatively large loss would be a matter of some concern in that biases might result in the data additional to those stemming from the use of an autopsied population, a special effort has been made and is being continued to reduce the proportion of necropsies without interviews. A loss of approximately 13 per cent, however, is considered definite. Refusals by physicians and repeated refusals by respondents account for 2 per cent, while the majority, 11 per cent, are patients for whom no apparently competent and informed relative could be located. A low success rate is, of course, anticipated within the remaining group (6 per cent) still pending in the renewed follow-up. This group includes, for example, some patients whose relatives declined interview permission during the earlier period, and others for whom no qualified relative could be found by routine methods. In addition, unfortunately, it will no longer be possible to find some potential respondents who were previously traced or traceable. Some degree of success, however, is being achieved in this follow-up effort, particularly within a group of relatives who were not approached previously because they resided at too great a distance to justify the cost of a personal visit. These are currently being interviewed by telephone.

ANALYSIS OF THE DATA

The pathologic and epidemiologic data are expected to yield evidence regarding hypothesized associations between variables in the two sets of data. Internal comparison constitutes the method of analysis, that is, comparison among subgroups within the population autopsied. Differentiation within this

*During this period, 2,574 deaths occurred among patients aged 15 and over in the Albany Hospital, of whom 62 per cent, or 1,586, came to autopsy. The difference between the 1,586 autopsies and the study population of 1,296 consists of 290 individuals, apparently unselected, whose hearts were dissected by the prosector in a manner that did not permit the special examination of the coronary arteries.

population is based primarily on two types of criteria. In one set of analyses the study population is dichotomized according to the presence or absence of myocardial infarction. In the second, atherosclerosis is expressed as a continuous variable: the mean wall thickness of the three major coronary arteries is used

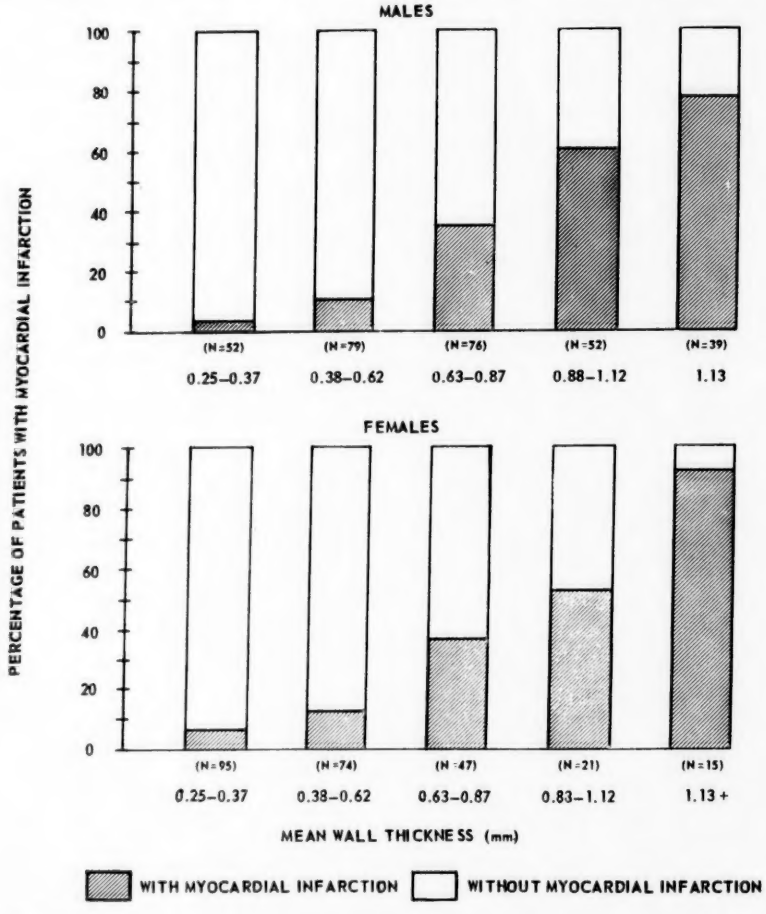

Fig. 2.—Percentage of patients with myocardial infarction acute or healed according to the mean wall thickness of the coronary arteries: 550 consecutively autopsied patients who died of any cause, Albany Hospital, 1955, to 1957.

to distinguish among individuals who range from those with severely thickened artery walls, to those with intermediate grades of thickening, to those with no abnormal thickening. The autopsied population is classified by the epidemiologic variables, and subgroups are compared according to (a) proportion with myocardial infarction, and (b) mean artery wall thickness.

Analyses of certain relationships among the pathologic variables are, of course, important in themselves, that is, without regard to epidemiologic characteristics. For example, the relationship between amount of atherosclerosis and

myocardial infarction and/or thrombosis is being assessed. Preliminary evidence pertaining to infarction, a relationship of direct concern to the underlying assumption of the study, as discussed earlier, is presented in Fig. 2. The occurrence of infarction is shown in relation to the mean wall thickness of the three major coronary arteries.* The association of the two events is strikingly apparent.† Among individuals in whom little or no wall thickening was detected (mean thickness of 0.25 mm. to 0.37 mm.), the proportion with infarction was approximately 5 per cent; while, by contrast, among those with greatest thickening (1.13 mm. and over), the proportion with infarction exceeded 75 per cent among males and 90 per cent among females. Each of the three wall thickness categories between these extremes displayed a stepwise increase in the proportion of individuals with infarction, thus adding consistency of trend to the evidence favoring the association. Similar patterns of association were found when each of three age groups was analyzed separately. Additional evidence regarding the association of infarction with coronary artery disease is to be presented in detail in a subsequent report.

One remaining area of the analyses which may be noted is that of relationships between the clinical and the pathologic data, for example, the amount and location of atherosclerosis may be associated with some electrocardiographic patterns not clearly understood at present.

Certain practical problems deserve mention regarding the size of the population required for projected analyses. An association between coronary artery atherosclerosis and some other variable may, of course, be grossly apparent in a relatively small study population. For example, the association between degree of coronary artery wall thickening and the presence of infarction was suggested in data pertaining to 264 patients collected during the first year of the study. However, when an association has been found in this "gross" sense, it needs to be more completely explored. To this end, it seems desirable to subdivide the "gross" tabulation according to a series of other variables in order to control factors presumed likely to bias the relationship (e.g., age, sex, the presence of "complicating" conditions). In addition, in the analyses of relationships between pathologic and epidemiologic data, it appears necessary to study the interactions among several epidemiologic variables, each of which is suspected of playing a part in what may be a multiple etiology (e.g., physical activity, fat consumption, chronic emotional stress, smoking). The final subgroupings resulting from a series of subdivisions designed to control certain characteristics and study some

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*The mean thickness of a single vessel was computed as follows from the data gathered during the first 2½ years:

$$t(0.25) + \left[(1 - t) \frac{1}{n} \sum_{1}^{n} \frac{a_i - b_i}{2} \right]$$

where t = proportion of total artery length characterized as "thin wall" (thickness = 0.25 mm.)
a_i = external diameter at site i
b_i = internal diameter at site i
n = number of sites (i) measured.

A patient's mean artery wall thickness is the sum of the single vessel means divided by three. Considerations underlying this and other methods of assessing atherosclerosis are discussed in a separate report on pathology methods now in preparation.

†By the chi square test, $p < .001$.

two or three of the epidemiologic variables in combination would contain very few individuals if the total study population were not large. To achieve such intensive analyses with subgroupings of a size which would lend confidence to interpretations, the collection of data regarding Albany Hospital autopsies will be continued, and, possibly, the study will be replicated at other institutions.

DISCUSSION

The use of an assessment of the extent of atherosclerosis in the coronary arteries as a means of studying coronary heart disease presupposed a close positive association between the two conditions. To test this assumption, an examination was made of the relationship between artery wall thickness, as a measure of atherosclerosis, and myocardial infarction, as an indicator of coronary heart disease. Although the relationship requires further, more detailed exploration, these data clearly serve to substantiate the original assumption, and thus to justify the approach adopted in the study design.

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Studies in England by Morris,[6] however, have raised some doubt as to whether an association does exist between atherosclerosis in the coronary arteries and infarction in the myocardium. It is difficult to compare Morris' data with those presented here, since the approach employed by Morris differed considerably from that of the present study. In the latter, the concurrence of infarction and atherosclerosis within single individuals is the crucial issue, while Morris' analysis dealt with the concomitance in time of two rates: the annual frequency with which severe atherosclerosis in the coronary arteries was reported in autopsy records in relation to the annual frequency with which myocardial infarction was described. He found, in brief, that severe atherosclerosis, as indicated chiefly by the term "calcification," was less frequently recorded in recent years as compared with earlier periods, beginning in 1908; while infarction was noted more frequently during recent years. The inference drawn was that the two conditions are unrelated.

It does not seem justifiable, however, in spite of Morris' findings, to discard the hypothesis that atherosclerosis and infarction are directly related, since evidence for the relationship appeared so clearly in the data of the present study. The methodologic advantage of assessing the association of the two events within the same individual lends increased confidence to the conclusion that the particular aspect of atherosclerosis studied here, namely, artery wall thickness, is indeed associated with infarction. It may be that other aspects of the disease are not so associated, such as the chief indicator of the disease employed by Morris, calcification. Special explorations, however, will be required to find an explanation of these divergent results.

That the mechanical effects of atherosclerosis, coronary stenosis, and occlusion could lead to infarction is highly plausible thus lending considerable support to the positive evidence for the association. On the other hand, we lack the more precise types of proof that might result from knowledge of the specific cause of atherosclerosis, or from greater success in the experimental production of the disease complex. Because of the present limited state of knowledge, an

examination of this relationship by means of quantitative data that are as detailed, precise, and complete as practicable should be of help in clarifying the extent to which atherosclerosis is operative in clinical coronary heart disease. Other features that may complicate the relationship remain, of course, to be assessed: acute thrombosis, intramural hemorrhage, collateral circulation.

For the purpose of studying the effects of epidemiologic variables hypothesized as playing a part in the etiology of the disease, an estimate of the mass or volume of disease present in the walls of the coronary arteries was desirable. This approach differs to some degree from that of more clinically oriented studies in which the remaining lumen size is more commonly emphasized. The basic aim of this study, however, is to employ an indicator of the amount of disease that will reflect the amount of reaction by the host to hypothetically injurious agents or activities. Even though lesions in the walls of the coronary arteries are a complex mixture of substances occupying space differentially, it seemed appropriate to strive for an estimate of the gross volume of these lesions as a first approximation of this reactivity.

In the epidemiologic phase of the study, the problem was to measure varying degrees of exposure to these hypothetically injurious agents expressed as patterns of activity or behavior. This was an ambitious aim, particularly when the information was to be collected "second-hand" from a relative of the subject. Like that of most epidemiologic studies of chronic disease, the primary objective was to determine certain characteristics of the life-styles of the individuals under study, in order to compare "cases" with "noncases" in these respects.

The epidemiologist will recall the many difficulties that may occur in obtaining valid interview information in the investigation of a communicable disease outbreak, even though such interviews are typically directed toward only a recent and limited time interval, often the preceding month. Considering the inaccuracies and misinterpretations that frequently arise in gathering such circumscribed data, it may seem overly ambitious to have attempted an estimate of an individual's long-term exposure, in some instances covering the full span of his life, to agents as ubiquitous as, for example, fat in the diet or physical energy expended in daily activities. A number of studies that utilized estimates of lifetime exposure or behavior, however, have yielded rewarding insights into certain diseases: occupational studies have been successful in establishing associations between exposure and illness, as, for example, radium dial painting and sarcoma of the jaw.[10] Smoking history has been shown to be associated with lung cancer[11,12] and heart disease.[12] Residence history has been helpful in establishing associations between fluorides in the natural water supply and dental caries,[13] and between geographic area and infection in histoplasmosis[14] and in coccidioidomycosis.[15] There was some basis, therefore, for anticipating that a carefully designed questioning procedure might successfully differentiate among patterns of exposure, both in terms of usual degree or frequency, and, more grossly, in terms of trends through time.

This study and similar epidemiologic inquiries into the etiology of certain chronic diseases thus place unusual demands upon the interview procedure. Special requirements exist with regard to precision and consistency; and specific

areas of interest, such as dietary intake and chronic emotional stress, present formidable difficulties. To conduct the methodologic explorations necessary, the skills of the sociologist in survey research methods appeared highly appropriate. One of the authors (R. U. M.) is undertaking these explorations.

It is scarcely necessary to point out that any population of autopsied individuals is a selected group. The bias resulting from death alone precludes any expectation of representativeness, and, in addition, hospitalization and consent for autopsy compound the selection process still further. Efforts have been made in some pathology studies to avoid the latter by limiting attention to accidental deaths alone,[16] but such study groups are, of course, subject to other forms of bias. Lack of representativeness has been accepted in this study as a necessary complexity because of the advantage of directly studying pathologic changes in relation to epidemiologic variables. The special limitations in hospital and autopsy study populations that have been pointed out by Berkson[17] and Mainland[18] are not to be taken lightly. The selective factors referred to above, as well as others that are presumed to exist in this population, are, however, too numerous and complex for individual discussion in this general report. A report now in preparation deals with comparisons among the study population, all Albany hospital deaths, and all Albany county deaths during a 4-year period. Elements of bias that may enter into any particular comparison, such as atherosclerosis and history of residence, or atherosclerosis and history of physical activity, will be examined in detail insofar as possible when data on these matters are reported.

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Certain procedures are being utilized to measure and, when possible, to control bias in making comparisons among subgroups within this autopsied population. It has been assumed that selective factors either are acting equally within each subgroup, or that when one is not equally distributed, it is likely to be identifiable and may be assessed or controlled by additional tabulations.

In an attempt to eliminate the possible bias of special factors, subgroups of the total population are being selected for analysis that are free of the characteristic under suspicion. Such a characteristic is the patient's (or relative's) knowledge that a clinical diagnosis of coronary heart disease was made, because of its possible influence upon other variables, such as occupation, residence, or diet, either as an influence on the patient's actual behavior, or on reporting by the patient (or relative) with regard to this behavior. This bias is being avoided to some degree by making epidemiologic comparisons (e.g., occupation) within a group of patients whose cardiac status was clinically unknown during life, since, at autopsy, a portion of this group exhibited severe atherosclerosis of the coronary arteries, and some, infarction. If, in analyses employing this special group, an association persists between degree of atherosclerosis and the epidemiologic variable under examination, the association could not reasonably be attributed to the effect on the patient of the knowledge that he had coronary heart disease. Nor, therefore, would such knowledge have affected the responses of relatives. Since neither the relative nor the interviewer is familiar with the pathologic findings, these interviews have the unusual advantage of being conducted "blind," a refinement frequently not possible in a retrospective study.

Thus, recognizing the more likely sources of selection in this study population, it is anticipated that, with careful exploration of each relationship, evidence will be forthcoming that is at least persuasive, if not conclusive, in support of an association or lack of association between a given variable and atherosclerosis and/or infarction.

In conclusion, the object of this report has been to describe: (1) the design of the study together with the considerations which led to this design, (2) the methods employed, (3) the limitations and special methodologic problems of the approach, as well as the various means adopted to deal with these, and (4) the types of analyses appropriate to the design, including an example from the pathologic data.

As was indicated, numerous alterations and refinements were instituted as the study proceeded, and many problems are still under exploration. However, in spite of its limitations and the problems initially anticipated, the study described has proved to be operable, and, from preliminary results, potentially valuable.

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SUMMARY

This is the first of a series of reports regarding an epidemiologic and pathologic study of coronary artery atherosclerosis. The reasons for inaugurating the study are described, together with the design and procedures found appropriate for its operation. Among consecutively autopsied patients who died of any cause, a quantitative estimate of coronary artery atherosclerosis has been made, and, by interviewing a close relative of each patient, information has been obtained about certain of his patterns of behavior or exposure during life. Relationships between degree of atherosclerosis and frequency or intensity of these activities or exposures during life are being examined within this population.

During a 4-year period, 1,296 individuals examined post mortem have been so studied. Preliminary analysis of the relationship between thickening of the wall of the coronary arteries and the occurrence of myocardial infarction indicates a close association between these two, thus justifying the use of atherosclerosis as a crucial measure of coronary heart disease.

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VALIDITY OF 70 MM. PHOTOFLUOROGRAMS OF THE CHEST IN SCREENING A POPULATION FOR HEART DISEASE

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INTRODUCTION

MINIFILM roentgenography of the chest has been a valuable screening technique for the discovery of tuberculosis in population groups. Anderson[1] has stated that minifilm roentgenography will continue to be useful in this regard, but that the technique must yield other benefits to justify mass application because of the reduced prevalence of tuberculosis. Screening programs for diseases of the heart have been considered by many investigators.[2-12]

Many of these studies have reported the results of cardiac examinations of persons with abnormal film findings among participants in mass surveys. In this type of study, persons with normal roentgenograms who have diagnosable heart disease (false negatives) are not identified. In general, the level of reading for cardiovascular abnormalities (percentage of films interpreted as abnormal) has been low and variable, ranging from 0.3 to 7.4 per cent. The higher levels of reading have resulted when a special effort was made to have the interpreters of roentgenograms note abnormalities in the cardiovascular shadow. The percentage of persons who were suspected of having cardiovascular disease, and in whom the presence of heart disease was confirmed, has also varied markedly, although follow-up has been poor in some studies.

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TABLE I. AGE DISTRIBUTION OF 2,252 PARTICIPANTS IN THE LOS ANGELES HEART STUDY, BY SEX

AGE (YEARS)	ALL PERSONS		MEN		WOMEN	
	NO.	%	NO.	%	NO.	%
Under 20	4	0.2	—	0	4	1.0
20–29	368	16.3	273	14.7	95	24.2
30–39	554	24.6	461	24.8	93	23.7
40–49	554	24.6	447	24.0	107	27.2
50–59	538	23.9	462	24.8	76	19.3
60–69	231	10.3	213	11.5	18	4.6
70	3	0.1	3	0.2	—	0
Total	2,252	100.0	1,859	100.0	393	100.0

Other studies to evaluate roentgenography as a screening technique have been conducted among groups in which the cardiac status of each person is known, permitting identification of persons with false-negative as well as false-positive roentgenograms. Slattery[11] reported the results of 682 "microfilms" of hospital outpatients, among whom 56 (8.2 per cent) were known to have heart disease. The level of reading was 5.4 per cent. Among the 56 patients with known heart disease and the 626 films which showed normal hearts, 45 per cent of the patients and 2 per cent of the films were read as positive for cardiovascular abnormalities.

In another hospital outpatient population, 23 per cent of whom had heart disease, Kurlander, Hill, and Enterline[6] reported roentgenographic abnormalities in 48 per cent of the persons with diagnosed heart disease or hypertension, and in 8 per cent of the persons with normal hearts.

A level of reading of 24 per cent has been reported by Brodeur, Baker, and Enterline [2] in a population of business executives and their families who received periodic physical examinations. In the group with diseased hearts and in that with normal hearts, 53 and 21 per cent of the films, respectively, were read as positive.

Our report describes the relationship of the diagnoses of the Los Angeles Heart Study population to the independent interpretations by two film readers of 70-mm. photofluorograms of the chest.

METHOD OF STUDY

The population is a sample of Los Angeles civil service employees working for the city in 1949. Although a random sample of employees, stratified by age and sex, was chosen for study, some persons in the sample refused to participate or were otherwise not available. Alternates were chosen for these individuals. The study participants are believed to be representative of city employees available and willing to participate in a study of diseases of the heart. The number of participants, by age and sex, is presented in Table I. Eighty-three per cent of these persons are men. Eighty-four per cent are white, 15 per cent are Negro, and 1 per cent are Oriental.

Each of the 2,252 individuals received a cardiac examination on entry to the study between December, 1949, and July, 1951. Included in the examination were a questionnaire history, physical examination, 70 mm. photofluorogram, fluoroscopy of the chest, electrokymogram, electrocardiogram, and a series of laboratory tests. The examination has been described in detail elsewhere.[8] Diagnoses of heart disease were based upon criteria of the New York Heart Association.[13] In this population, 7.3 per cent had diagnoses of heart disease, and 3.6 per cent of possible or potential heart disease.

At the time of the clinical examinations the minifilms were interpreted by chest physicians who were reading primarily for tuberculosis. Cardiovascular abnormalities were reported observed in less than 1 per cent of the films, and these findings did not contribute greatly to the diagnosis of heart disease.[8]

For purposes of the present study, the 70 mm. films were reviewed by two of the authors (G. J., W. J. R.), each of whom read independently of the other and without knowledge of the clinical status or other characteristics of the individuals examined. One reader is a radiologist, and the other is a specialist in tuberculosis. Each was asked to record all cardiovascular abnormalities observed, regardless of the reader's impression of the clinical significance of the abnormality. In this report the readers are designated "A" and "B", each representing the same individual throughout.

TABLE II. PREVALENCE OF CARDIOVASCULAR ABNORMALITIES ON 70 MM PHOTOFLUOROGRAMS

FILM FINDING	READER A		READER B	
	NO.	%	NO.	%
Heart:				
Enlargement, over 20%	62	2.9	22	1.0
Enlargement, 10–20%	327	15.4	168	7.9
Other abnormalities	——	0	26	1.2
Aorta:				
Calcified	3	0.1	11	0.5
Tortuous	242	11.4	71	3.3
Widened	332	15.7	49	2.3
Prominent knob	22	1.0	67	3.1
Other	——	0	4	0.2
Other great vessels and lungs	10	0.5	33	1.5
No cardiovascular abnormality	1,432	67.5	1,779	83.4
All observed satisfactory films	2,120	100.0	2,134	100.0
Unsatisfactory film	13		13	
Not observed	119		105	
All persons	2,252		2,252	

RESULTS

The roentgen findings are presented in Table II. Because each reader recorded more than one abnormality observed in some films, the sum of the percentages in Table II (based on observed films) exceeds 100. Films for some persons ("not observed") could not be located or were nonexistent. Among the noncardiovascular abnormalities noted by reader A were 84 cases of suspected

reinfection tuberculosis, 38 of which were recorded as active or were suspected to be active cases. Reader B noted the same abnormality on 38 films, of which 29 were recorded as showing "activity" or "suspected activity." Each reader observed 4 neoplasms of the lung.

For the purpose of assessing the validity of the film interpretations, when 2 or more cardiovascular abnormalities were observed on a single film, classification was made according to only one of these findings. The order of priority is the same as the order in which roentgen abnormalities are listed in Table II. For example, when both an enlarged heart and a calcified aorta were noted on a film, the findings were classified as "heart enlargement" only. All film findings presented herein, except those in Table II, are classified according to this priority scheme.*

In this report the term "positive film" refers to a film on which any cardiovascular abnormality was observed, unless specified otherwise. In the presentation of results the percentages of positive films within the diseased and nondiseased segments of the population are compared, with recognition of the desirability of a low percentage of positive films in the normal group and a high percentage of positive films among the persons with heart disease.

Table II summarizes the results of x-ray interpretations by each reader among persons with and without heart disease. Reader A recorded cardiovascular abnormalities in 688 of the 2,120 observed films, a level of reading of 32.5 per cent. Clinically, 153 of the 2,120 persons represented by these films had heart disease, 1,889 had normal hearts, and the other 78 had possible or potential heart disease. Abnormalities were recorded by Reader A in 71.2 per cent of the persons who had a diagnosis of heart disease, and in 28.8 per cent of those who had normal hearts. No abnormalities were noted in 28.8 per cent of the persons with heart disease ("missed" cases).

Reader B observed 2,134 films and recorded cardiovascular abnormalities in 355, a level of reading of 16.6 per cent. These abnormalities were recorded in 49.4 per cent of the persons with heart disease, and in 13.8 per cent with normal hearts. No cardiovascular abnormality was recorded in 50.6 per cent of the persons with heart disease.

In summary, reader A, who observed cardiovascular abnormalities in nearly one third of the population screened, identified more than 70 per cent of the cases of heart disease and the same proportion of clinically normal cases. Reader B, who observed abnormalities in 17 per cent of the population, identified approximately half of the cases of heart disease and 86 per cent of the normal cases (See Table III).

Abnormalities of the aorta (without enlargement of the heart) noted by reader A were of little or no value in identifying clinical cases of heart disease in this study population. Reader A, for example, among 153 persons with heart disease, recorded 24 films (15.7 per cent) as positive on the basis of aortic abnormalities only (calcified, tortuous, widened, or prominent arch), about the

*This method of classification was employed by Brodeur, Baker, and Enterline,[2] who made available the abnormality code used in their study.

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same proportion positive as in 1,889 persons with clinically normal hearts (Table IV). Since the same proportion of persons had positive films in both the diseased and the nondiseased segments of the population, the criterion for positive film as interpreted by reader A proved to be invalid because it failed to distinguish between the diseased and nondiseased segments of the population under study.

Contrary to the results for reader A, however, abnormalities of the aorta observed by reader B appear to have had some validity in screening persons for heart disease. Reader B recorded 16.8 per cent of the films of persons with heart disease as positive on the basis of abnormalities of the aorta, as compared to 4.9 per cent positive among persons in the normal group. In view of these findings, the validity of roentgenographic screening of heart disease in this population is based primarily on the finding of an enlarged heart (Table IV). This observation was made for each etiological type as well as for the total number of persons with heart disease. Among the etiological types, hypertensive heart disease was identified with the greatest relative frequency. Reader A recorded cardiovascular abnormality in 72 of 90 cases (80 per cent), and reader B, in 54 of 90 cases (60 per cent). As noted above, this is due largely to the finding of an enlarged heart, rather than other cardiovascular abnormalities. Enlargement of the heart was recorded by reader A in 64.5 per cent of the patients with hypertensive heart disease, and by reader B in 36.7 per cent, as compared with 14.9 and 6.8 per cent, respectively, in the normal group (Table IV).

A relatively high frequency of positive films is noted among persons with coronary heart disease. Approximately half of the 50 patients classed as having coronary heart disease had both coronary and hypertensive heart disease. Because of this association, coronary and hypertensive heart disease are subdivided, with the results shown in Table V. The relatively high frequency of positive films in patients with coronary disease occurred mainly in the group of patients who had combined coronary and hypertensive heart disease. The readers recorded the same number positive, age for age, among persons with coronary disease (without hypertensive heart disease) as among persons who were clinically normal. Hence, there was little or no validity in the screening of coronary heart disease in this population group except among patients with coronary disease who also had hypertensive heart disease.

TABLE III. CARDIOVASCULAR ABNORMALITIES OBSERVED BY FILM READER ON 70 MM. PHOTOFLUOROGRAMS IN PERSONS WITH HEART DISEASE AND THOSE WITH NORMAL HEARTS

	TOTAL POPULATION		HEART DISEASE		NORMAL HEART		POSSIBLE HEART DISEASE	
	NO.	%	NO.	%	NO.	%	NO.	%
Reader A	2,120	100.0	153	100.0	1,889	100.0	78	100.0
Positive	688	32.5	109	71.2	544	28.8	35	44.9
Negative	1,432	67.5	44	28.8	1,345	71.2	43	55.1
Reader B	2,134	100.0	154	100.0	1,902	100.0	78	100.0
Positive	355	16.6	76	49.4	262	13.8	17	21.8
Negative	1,779	84.4	78	50.6	1,640	86.2	61	78.2

TABLE IV. RESULTS ACCORDING TO TYPE OF ROENTGEN ABNORMALITY BY ETIOLOGICAL CLASSIFICATION OF HEART DISEASE

ETIOLOGICAL TYPE OF HEART DISEASE AND FILM FINDING	READER A		READER B	
	NO.	%	NO.	%
Total with heart disease	153	100.0	154	100.0
Heart enlarged	85	55.6	50	32.5
Abnormal aorta	24	15.7	26	16.9
No cardiovascular abnormality	44	28.8	78	50.6
Hypertensive heart disease	90	100.0	90	100.0
Heart enlarged	58	64.5	33	36.7
Abnormal aorta	14	15.6	21	23.3
No cardiovascular abnormality	18	20.0	36	40.0
Coronary heart disease	50	100.0	50	100.0
Heart enlarged	27	54.0	15	30.0
Abnormal aorta	9	18.0	6	12.0
No cardiovascular abnormality	14	28.0	29	58.0
Rheumatic heart disease	21	100.0	22	100.0
Heart enlarged	12	57.2	10	45.5
Abnormal aorta	1	4.8	2	9.1
No cardiovascular abnormality	8	38.1	10	45.5
Other heart disease	21	100.0	21	100.0
Heart enlarged	9	42.9	4	19.0
Abnormal aorta	3	14.3	3	14.3
No cardiovascular abnormality	9	42.9	14	66.7
Possible or potential heart disease	78	100.0	78*	100.0
Heart enlarged	21	26.9	11	14.1
Abnormal aorta	14	18.0	5	6.5
No cardiovascular abnormality	43	55.1	61	78.2
Normal heart	1,889	100.0	1,902†	100.0
Heart enlarged	283	14.9	129	6.8
Abnormal aorta	258	13.7	93	4.9
Other great vessels	3	0.2	15	0.8
No cardiovascular abnormality	1,345	71.2	1,640	86.2

*Includes 1 film with other unspecified abnormality of the heart.
†Includes 25 films with other unspecified abnormality of the heart.

The observed and expected frequencies based on the hypothesis that the reader read the same proportion positive in each 10 year age group of persons with coronary disease as in the normal heart group are as follows:

READER A	EXPECTED FREQUENCY	OBSERVED FREQUENCY
Coronary only	14.4	16
Coronary and hypertensive	12.8	20
Hypertensive only	30.8	49
READER B		
Coronary only	6.8	7
Coronary and hypertensive	5.9	14
Hypertensive only	14.0	37

The expected and observed frequencies are nearly equal for coronary heart disease. In hypertensive heart disease the observed frequencies of positive films exceed those expected.

Among 58 persons with hypertensive heart disease who had a positive film on the basis of an enlarged heart, reader A recorded that in 15 (26 per cent) the heart was enlarged by more than 20 per cent, and in the other 43 it was enlarged by 10 to 20 per cent. Of those who had positive films according to reader B, 6 of 27 were recorded as having an enlargement of more than 20 per cent, and the other 21 had an enlargement of 10 to 20 per cent. Therefore, of those with positive films, not more than one fourth had an enlargement greater than 20 per cent. If one restricted screening of individuals to enlargement of this degree, a much larger proportion of the cases in the population would be missed than in screening at the level of 10 per cent or more enlargement.

TABLE V. POSITIVE FILMS IN CORONARY AND HYPERTENSIVE HEART DISEASE*

ETIOLOGICAL CLASSIFICATION AND FILM FINDING	READER A		READER B	
	NO.	%	NO.	%
Hypertensive heart disease only	62	100.0	62	100.0
Heart enlargement	38	61.3	22	35.5
All cardiovascular abnormalities	49	79.0	37	59.7
Coronary heart disease only	26	100.0	26	100.0
Heart enlargement	10	38.5	5	19.2
All cardiovascular abnormalities	16	61.5	7	26.9
Coronary and hypertensive heart disease	24	100.0	24	100.0
Heart enlargement	17	70.8	10	41.7
All cardiovascular abnormalities	20	83.3	14	58.3

*Four cases of hypertensive heart disease combined with etiological types other than coronary are excluded.

Newly Discovered Cases.—In appraising the value of screening programs it is desirable to group those persons in whom the findings are positive into "newly discovered cases" and "previously known cases." At the time of the initial cardiac examination of the Los Angeles Heart Study population, each person was asked whether he had ever been told by a doctor that he had any of the following conditions: heart murmur, heart valve trouble, rheumatic heart trouble, heart failure, coronary thrombosis, heart attack, or enlarged heart. Persons with heart disease who answered affirmatively, regardless of the condition specified, were classed as "old cases." Persons with heart disease and negative or unknown histories were classed as "newly discovered cases." As noted above, reader A recorded a cardiovascular abnormality in 109 of 153 persons with heart disease. Of the 109 positives, 75 (69 per cent) were new, and 34 (31 per cent) old cases according to the criteria used. Of 76 positive by reader B, 52 cases (68 per cent) were new and 24 (32 per cent) old. As expected, enlargement of the heart of more than 20 per cent was somewhat more selective of previously known cases. It is

recognized that a screening program, in addition to detecting new cases, may also benefit old cases if they are returned to medical care.

Age Distribution Analysis.—Although only one fifth of the persons in this study were over 55 years of age, half of the cases of heart disease were in this age group. In the age distribution analysis of x-ray findings a higher proportion of positive films is noted among persons with clinically normal hearts who are 55

TABLE VI. MINIFILM RESULTS* AMONG PERSONS WITH NORMAL HEARTS AND PERSONS WITH HEART DISEASE, BY AGE

AGE (YEARS)	READER A		READER B	
	NO.	%	NO.	%
18-29				
Normal heart	337	100.0	340	100.0
Positive	21	6.2	24	7.1
Negative	316	93.8	316	92.9
Heart disease	4	100.0	4	100.0
Positive	1	25.0	1	25.0
Negative	3	75.0	3	75.0
30-54				
Normal heart	1,209	100.0	1,216	100.0
Positive	308	25.5	131	10.8
Negative	901	74.5	1,085	89.2
Heart disease	67	100.0	68	100.0
Positive	44	65.7	31	45.6
Negative	23	34.3	37	54.6
55-70				
Normal heart	343	100.0	346	100.0
Positive	215	62.7	107	30.9
Negative	128	37.3	239	69.1
Heart disease	82	100.0	82	100.0
Positive	64	78.0	44	53.7
Negative	18	22.0	38	46.3

*Based upon all cardiovascular abnormalities.

to 70 years old than among those who are 30 to 54 years old (Table VI). In the normal group, reader A recorded 25 per cent positive among persons who were 30 to 54 years old, and 63 per cent positive among those who were 55 to 70 years old. The proportion found to be positive by reader B in the clinically normal group increased from 11 per cent in the 30 to 54 year age group to 31 per cent in the 55 to 70 year age group. In contrast to the marked increase in the percentage positive in the normal group, a relatively small increase in the percentage positive is observed in persons with heart disease who are 55 to 70 years old, as compared to those who are 30 to 54 years old. Among persons with heart disease, reader A recorded 65.7 per cent positive in the 30 to 54 year age group, and 78 per cent positive in the 55 to 70 year age group. Positive films were recorded by reader B in 45.6 per cent of the patients with heart disease who were 30 to 54 years old, and in 53.7 per cent of those who were older.

The results derived from Table VI suggest that a program of screening a similar population which was over 30 years of age might lead to the identification of one half (reader B) to two thirds (reader A) of the cases of heart disease, according to the criteria used. However, of the total number of positive films according to these criteria (any roentgenographic cardiovascular abnormality regardless of suspected significance), 76 to 83 per cent would be recorded in persons without other clinical evidence of heart disease—i.e., in the group of persons who had normal hearts. Because some positive films in this study may not have been considered significant for follow-up, and hence not reported in the usual x-ray survey, the results should not be related directly to community case-finding programs. Studies such as this, however, provide some insight into the validity of 70 mm. photofluorography case-finding programs.

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Because the prevalence of heart disease is greater in older persons, it will be realized that age, in itself, should have some validity in screening for heart disease. That is, a procedure in which "positives" are defined as all persons older than a given advanced age will be selective for heart disease. This procedure, using age 50 as the criterion for "positive," has been applied to persons whose films were observed by reader A. The resulting "level of reading" (proportion over the age of 50 years) is 34.1 per cent, which is approximately equal to the level at which reader A recorded roentgenographic cardiovascular abnormalities.

Of the persons over 50 years of age ("positive" on age), 14.7 per cent had heart disease, 79.9 per cent had normal hearts, and the remainder had possible or potential heart disease. Age as a criterion may be compared with the minifilm findings at a high level of reading (reader A). Of the total number of persons with positive films, 15.8 per cent had heart disease and 79.9 per cent had normal hearts. This suggests that cardiovascular abnormalities noted at a high level of reading (32.5 per cent) were only about as valid in the identification of diagnosed heart disease in this population as was age alone. It should be emphasized, however, that cases "identified" on the basis of age are not the same cases identified on minifilm screening. Using the criteria of "55 years and over," "60 years and over," and "over 65 years," age as compared to roentgenography is progressively poorer in the "identification" of heart disease.

TABLE VII. CRITERION FOR POSITIVE FILM

DIAGNOSIS AND FILM FINDING	HEART ENLARGEMENT		ALL CARDIOVASCULAR ABNORMALITIES	
	No.	%	No.	%
Normal heart	1,887	100.0	1,887	100.0
Positive	92	4.9	191	10.1
Negative	1,795	95.1	1,696	89.9
Heart disease	153	100.0	153	100.0
Positive	46	30.1	73	47.7
Negative	107	69.9	81	52.3

Positive Films by Two Readers.—Films on which cardiovascular abnormalities were observed by both readers are tabulated according to two criteria: heart enlargement and all cardiovascular abnormalities. The results are shown in Table VII.

When all cardiovascular abnormalities were used as the criterion for a positive film, compared to heart enlargement as the criterion, the number of positives among normal persons doubled, and the positives among persons with heart disease increased from 46 to 73. Of 138 persons with positive films on the basis of enlargement of the heart, in 46 (one third) heart disease was confirmed and in 92 (two thirds) a normal heart was diagnosed.

Subsequent Status of the Population.—Information is available on the status of the Los Angeles Heart Study population subsequent to the entrance examination diagnoses on which the foregoing results are based. Most participants received two additional clinical examinations at intervals of 12 to 18 months. Information is also available on deaths which occurred among the participants. It is possible, therefore, to study the minifilm findings according to the subsequent status of the individuals in order to determine whether the initial roentgenographic examination was selective for individuals who were found to have a normal heart, but who later acquired heart disease, or who died of heart disease. The study population is divided into four groups, or cohorts, according to the status on first and later examination. These are as follows:

	ENTRANCE EXAMINATION	SUBSEQUENT STATUS
Group I	Normal heart (1,889)	Normal heart (1,652)
		Noncardiovascular death (14)
		Not examined (223)
II	Normal heart (118)	Heart disease (118*)
III	Heart disease (47)	Normal heart (47)
IV	Heart disease (203)	Heart disease (179†)
		Not examined or noncardiovascular death (24)

*Includes 13 deaths.
†Includes 11 deaths.

Of those persons who had normal hearts at the time of the entrance examination, but who later developed heart disease or who died of heart disease (Group II), a higher percentage had cardiovascular abnormalities on the entrance examination minifilm than did persons who remained normal (Group I). The proportion of positive films is summarized in Table VIII. Reader A recorded 16.2 per cent positive on the basis of enlargement of the heart in Group I, and 29.4 per cent positive in Group II. The percentages positive reported by reader B were 6.8 per cent (Group I) and 15.7 per cent (Group II). An increase in percentages positive in Group II, as compared to Group I, is also noted when any cardiovascular abnormality is used as the criterion for a positive film. Because the persons in both Groups I and II were found to have normal hearts at the time of entry, the data suggest that not all of the "false" positives were actually false, and/or that some abnormalities noted by the readers may have been subclinical at the time of the first (entrance) examination, and subsequently advanced to a stage of clinical recognition. Since the differences observed between these two groups

are small, one cannot say from a screening and case-finding point of view that the photofluorogram was very selective for persons with normal hearts who were destined to acquire heart disease during the 30 month interval between the first and third clinical examinations.

DISCUSSION

The Los Angeles Heart Study provides an opportunity to evaluate the use of 70 mm. photofluorography of the chest and other screening techniques in the identification of diseases of the heart. The study is more representative of group screening than of mass screening, since it is limited to civil service employees. At the time of the initial examination of the study population the photofluorograms were read by physicians in a tuberculosis clinic who by practice were reading primarily for tuberculosis. Hence, the initial readings were akin to identifying suspected cases of heart disease "found" incidentally in the course of reading films for tuberculosis. In this study population the original single level of reading for cardiovascular abnormalities by the several available readers was less than 1 per cent and contributed little to the identification of the cases of heart disease.[8] Although referral of cardiovascular suspects "found" incidentally in the course of reading survey films for tuberculosis is probably necessary on moral or ethical grounds, our original experience did not confirm the value as a case-finding procedure.

The present study is based upon independent rereading of the films, with emphasis upon suspected cardiovascular abnormalities, regardless of significance and without reference to the opinion of the reader concerning need for referral. The resulting levels of reading, 32.5 per cent positive by reader A and 16.6 per cent positive by reader B, "identified" nearly three fourths (reader A) or nearly one half (reader B) of the cases of heart disease in the study population. The higher of the two levels of reading associated with the higher yield of cases was also associated with twice as many positive films among clinically normal persons as were found at the lower level of reading.

Because abnormalities of the aorta (without enlargement of the heart) did not distinguish between the clinically diseased and nondiseased in the population studied, and other types of abnormality were rarely encountered, it would appear appropriate that referral in x-ray case-finding programs be limited to those persons with suspected enlargement of the heart.

Since roentgenography is most selective for hypertensive heart disease among the etiological types, the ultimate benefit to the persons with this disease who is discovered or returned to treatment must be considered. Because persons with hypertensive heart disease who are discovered early might benefit most, the findings by age groups in this study are of interest. The sensitivity of the minifilm in the identification of persons in the 30 to 54 year age group was almost as good as in persons in the 55 to 70 year age group, and with proportionally fewer positives among persons who had clinically normal hearts.

Study of multiple screening, basing "positives" on the results of a combination of applicable screening techniques, should be undertaken to discover improved methods in case-finding.

TABLE VIII. PERCENTAGE OF POSITIVE FILMS ON ENTRANCE EXAMINATION ACCORDING TO SUBSEQUENT CLINICAL STATUS

GROUP	ENTRANCE EXAMINATION	SUBSEQUENT STATUS	NO. PERSONS	CRITERION FOR POSITIVE FILM			
				HEART ENLARGEMENT		ALL CARDIOVASCULAR ABNORMALITIES	
				READER A	READER B	READER A	READER B
I	Normal heart	Normal heart	1,889	16.2	6.8	31.9	14.1
II	Normal heart	Heart disease	118	29.4	15.7	55.9	33.3
III	Heart disease	Normal heart	47	34.2	5.4	57.9	18.9
IV	Heart disease	Heart disease	179	52.0	32.2	67.8	47.5

A decision for or against the mass use of screening techniques in community case-finding programs should consider, in addition to the scientific validity and applicability of the test, the ultimate benefit to the community and to persons in whom the disease is discovered. Screening programs are applied to apparently well persons, not to the obviously sick. It is generally believed that persons suspected of having rheumatic heart disease who are identified in screening programs and placed under supervision for prophylaxis and treatment benefit as a result of the screening program. There is relatively less benefit to persons with hypertensive and/or coronary heart disease discovered as a result of screening programs. Persons with frank heart disease, including coronary thrombosis, for whom medical care may be lifesaving are discovered because of acute symptoms rather than by screening programs. Certain persons with congenital heart disease benefit from operation. Blood-pressure screening for hypertension may prove valuable, although additional research is needed to evaluate results.

The type of heart disease discovered in a screening program depends upon the screening technique used and the prevalence of the etiological types of heart disease. Hypertensive and coronary heart disease are more prevalent among adult populations than rheumatic heart disease, congenital heart disease, and other etiological types. Screening programs among apparently well persons will identify more individuals with hypertensive heart disease (with and without coronary heart disease) than individuals with other types of heart disease who may benefit more by discovery. Organized control programs, directed toward a single etiological type of heart disease, such as rheumatic fever and rheumatic heart disease, may be of more benefit to the community and the individual than generalized screening of population groups for all types of heart disease.

SUMMARY

Minifilms of the chest taken routinely during the course of cardiovascular examinations of the Los Angeles Heart Study population were reread independently by two observers to assess the validity of the 70 mm. photofluorogram as a screening device for diseases of the heart. Roentgenographic cardiovascular abnormalities were recorded by the observers in 32.5 and 16.6 per cent of the

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study population. At the higher of the two levels of reading, 71.2 per cent of the persons with heart disease and 28.8 per cent of those who had normal hearts had "positive" films according to the criteria used. At the lower level of reading approximately half (49.4 per cent) of the clinically diagnosed cases of heart disease in the study population were "identified" by the minifilm, while 13.8 per cent in the clinically normal group had positive roentgenograms. A relatively small increase occurred in the proportion who were minifilm positive among diagnosed cases in the older (55 to 70 years) age group as compared to those in the 30 to 54 year group, this was in contrast to the sharp increase with age in the proportion with positive minifilms in the clinically "normal" group.

The validity of the roentgenographic screening was based primarily on the finding of heart enlargement and, of the etiological types, hypertensive heart disease was identified with the greatest relative frequency. Abnormalities of the aorta (without heart enlargement), when used as a criterion for "positive" film, had little or no validity in screening, for approximately the same proportion were positive in the clinically diseased as in the nondiseased segments of the study population. The relationship of the findings to group screening is discussed.

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THE CIRCULATORY RESPONSE TO SMOKING: THE EFFECT OF SMALL DOSES OF HEXAMETHONIUM AND OF MEPHENTERMINE ON THE PATTERN OF RESPONSE

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DURING a standard ballistocardiographic smoking test, many different types of circulatory response are found among healthy young adults.[1,2] Some subjects show hyperreactivity of the blood pressure, heart rate, or cardiac output in various combinations, while others with similar smoking habits show little change or even a negative response. The variations in circulatory reactivity undoubtedly reflect individual differences in homeostasis which may be of considerable importance, particularly in regard to susceptibility to future hypertension or coronary artery disease. In 1938, Herrell demonstrated that certain persons with "a tendency toward" hypertension showed dramatic rises of blood pressure after smoking a cigarette, and in the same year, Hines and Roth reported that the most marked elevation of blood pressure during a standard smoking test occurred among patients with essential hypertension.[3-5] We found that the degree of change in cardiac output in healthy medical students following smoking may be related to genetic factors.[1] Thus the offspring of hypertensive parents showed an exaggerated increase in cardiac output after one cigarette as well as a greater rise in blood pressure and heart rate when compared with the offspring of unaffected parents. On the other hand, the offspring of parents with coronary artery disease showed a more marked diminution in stroke volume and a much smaller increase in cardiac output after smoking than did the offspring of unaffected parents. Accordingly, differences in response to the smoking test may be of predictive value in regard to the development of hypertension or coronary disease at an early age, on the one hand, or as an index of longevity and relative freedom from cardiovascular disease on the other.

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Eight tables setting forth the detailed data and statistical analyses presented with this report have been omitted because of lack of space. These tables are available, from the authors, in mimeographed form to interested readers.

TABLE I. SCHEDULE OF INJECTIONS

SUBJECT NO.	STUDY NO.	AGE	HEIGHT (IN.)	WEIGHT (LBS.)	S.A.*		ORDER OF TESTS								
							1	2	3	4	5	6	7	8	9
1	59121	24	70.50	152.00	1.85	Substance	M	N	N	H	H	M	M	M	H
						Dose†	10	—	—	5	10	15	15	15	7.5
						Date	7/30	8/2	8/6	8/8	8/20	8/22	8/24	8/27	10/3
2	60134	23	72.00	182.25	2.02	Substance	M	H	N	M	M	H	H	N	—
						Dose	10	5	—	15	15	10	15	—	—
						Date	8/8	8/20	8/22	10/2	10/8	10/16	11/9	11/14	—
3	59142	24	69.00	153.50	1.82	Substance	M	M	N	—	—	—	—	—	—
						Dose	10	10	—	—	—	—	—	—	—
						Date	7/29	7/30	7/31	—	—	—	—	—	—
4	59143	23	71.50	166.00	1.94	Substance	M	M	N	H	H	M	N	H	—
						Dose	10	15	—	5	10	20	—	12.5	—
						Date	8/22	8/28	8/31	11/7	11/14	11/20	11/21	12/5	—
5	58153	24	76.00	185.50	2.13	Substance	N	H	H	M	M	N	—	—	—
						Dose	—	5	5	5	10	—	—	—	—
						Date	7/16	7/18	7/22	7/24	8/1	8/6	—	—	—
6	60147	27	76.50	168.00	2.04	Substance	N	H	M	M	H	N	H	M	—
						Dose	—	5	3	10	10	—	10	15	—
						Date	7/17	7/19	7/23	7/26	7/30	8/5	8/8	8/9	—
7	59158	21	66.75	143.00	1.73	Substance	M	H	M	N	N	H	H	M	—
						Dose	10	5	15	—	—	3	3	15	—
						Date	8/8	8/20	8/24	8/27	8/31	9/4	9/10	9/17	—
8	58171	24	69.50	175.00	1.95	Substance	N	H	M	M	H	N	M	H	—
						Dose	—	5	4	10	10	—	15	12.5	—
						Date	7/16	7/18	7/23	7/29	7/31	8/5	8/7	10/22	—
9	58172	24	68.50	170.00	1.92	Substance	N	H	M	N	M	H	M	H	—
						Dose	—	5	5	—	10	10	15	12.5	—
						Date	7/16	7/18	7/23	7/30	8/1	8/6	8/7	10/22	—

*S.A. — surface area in square meters. H—hexamethonium. M—mephentermine. N—control or placebo (isotonic salt solution).
†All dosages are expressed in mg. of the hexamethonium radicle or the mephentermine sulfate salt.

In order to investigate further these individual differences in circulatory homeostasis, it seemed worth while to attempt to change the response to smoking by modifying the physiologic state of the subject with different pharmacologic substances. In this way a start might be made toward a better understanding of the homeostatic mechanisms which predominate in a given individual. The first two pharmacologic substances chosen for study were hexamethonium chloride, a hypotensive agent which acts at full dosage levels through blockade of both sympathetic and parasympathetic ganglia, and mephentermine sulfate, a pressor substance which in human subjects is perhaps the most effective antagonist of hexamethonium.[6] Because the pharmacologic stimulus provided by smoking a single cigarette is relatively small, we were interested in first exploring the effect of minimal doses of these substances.

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METHOD

Nine white male medical students of the classes of 1958, 1959, and 1960 volunteered as subjects for the study during the summer of 1957. All were in good health and were 23 or 24 years of age except Subject 59158 who was 21, and Subject 60147 who was 27. Six were regular cigarette smokers (15 to 20 a day). Subjects 58171 and 58172 were identical twins who were both light cigarette smokers (less than 5 a day) and one (Subject 59143) was a nonsmoker. Subjects came to the laboratory at intervals of several days until the tests were completed.* In all, 66 tests were carried out, 17 with isotonic salt solution as a placebo, 23 with hexamethonium chloride, and 26 with mephentermine sulfate (Table I). At each visit, after control readings of blood pressure, heart rate, and ballistocardiogram were recorded by the technician, either hexamethonium chloride, mephentermine sulfate or a 0.9 per cent sodium chloride solution was injected intravenously by one of us (E. A. M.). The substance injected was always made up to a volume of 5 ml. At intervals of one minute 1 ml. doses were given until the total volume had been injected. During the injection, the blood pressure and pulse rate were measured every minute as a precaution against overdosage. After the injection, blood pressure and pulse rate readings were continued, and at the end of 5 minutes a second set of observations was recorded by the technician. The ballistocardiographic smoking test was then carried out as previously described.[1,2] A third set of measurements was recorded immediately after the subject had smoked a single cigarette. Neither the subject, the technician, nor the assistant who made the ballistocardiographic measurements knew which one of the substances had been given. Accordingly, this was a double blind experiment.

It was planned to perform 8 tests on each subject, 3 with each of the test substances and 2 with the placebo. Actually, 7 subjects completed the 8 tests (one of these had an extra mephentermine sulfate test). One subject had 6 tests (2 of each kind), while one subject lapsed after one placebo and 2 mephentermine sulfate tests. Tests with the 3 substances were performed in random order. The

*In some instances the series was interrupted for a number of weeks because the subject went on vacation (see Table I).

intervals between tests were sufficiently long to avoid the development of drug tolerance. Our aim both for hexamethonium chloride and mephentermine sulfate was to give a threshold dose rather than the maximum dose; therefore, the dosages were purposely kept small.

The initial dose of hexamethonium was 5 mg. in every instance.* On subsequent tests this dose was gradually increased save in the case of subjects showing an excessive reaction to the drug. The first 4 subjects receiving mephentermine sulfate were given doses of 5 mg. or less, but since this dosage seemed to have little if any effect, the initial dose was thereafter increased to 10 mg.

In this study, as in previous ones, "stroke volume" and hence "cardiac output" are based on the area under the I and J waves, and it is this variable which we are in fact measuring. The exact relationship between the area under the I and J waves and true stroke volume is still uncertain.

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RESULTS

Placebo Tests in Which Isotonic Salt Solution was Injected.—Examination of the individual data from the placebo tests showed that the injection of isotonic salt solution itself produced no significant changes; the very slight fall in most of the mean values after injection probably reflects the effect of continued rest and relaxation on the table. The mean changes after smoking a single cigarette were similar to those found in larger series of subjects.[1,2]

As we have previously pointed out, individual differences in the patterns of circulatory response to smoking are quite marked. The present small series illustrates these differences. For example, in Fig. 1, where the percentage changes after smoking are presented, Subject 1 shows well marked increases in systolic and diastolic pressure, heart rate, and cardiac output in the placebo tests, while Subjects 8 and 9, the twins, show little or no change. It is particularly noteworthy that the twins' heart rates do not rise on smoking; this is also true of Subject 2. Accordingly, it appears that various types of reaction patterns were included in the present series of 9 subjects as well as in the larger groups previously reported.

Eight subjects had 2 placebo tests each; the ninth had but one. In general the 2 tests showed a satisfactory degree of consistency with each other, although in some instances (as in the post-smoking heart rate of Subject 7) marked disagreement both in direction and magnitude of response occurred. Based on paired data, estimates of mean variation within subjects in response to the saline injection and to smoking were calculated. The values indicate, for example, that the systolic change after an injection of salt solution will differ from the parameter, or mean of an infinitely large number of tests on that subject, by 2.0 mm. Hg or less in two-thirds of the cases and less than twice that amount in 95 per cent of cases. These values for mean experimental error refer to mean variation in the test for the entire group and cannot be applied with confidence to individual subjects. As we have previously noted, variation within the individual

*Dosage of this drug is expressed as mg. of hexamethonium radicle. Hexamethonium chloride was used throughout, 73.67 per cent of which is hexamethonium radicle. Accordingly, to find the dose as chloride, multiply by 1.357.

differs widely from subject to subject.[2] For the subsequent comparisons we shall use the mean of the 2 placebo tests on each individual as the best estimate of the parameter for that subject.

The remainder of the paper is devoted to answering the questions; did the injection of the pharmacologic substances under study affect the circulatory response to smoking in any or all subjects, and in any or all dosages? In view of the differences found in the placebo tests in individual patterns of circulatory response to smoking, it would not be surprising if, when the normal physiologic equilibrium is modified by the administration of an active pharmacologic sub-

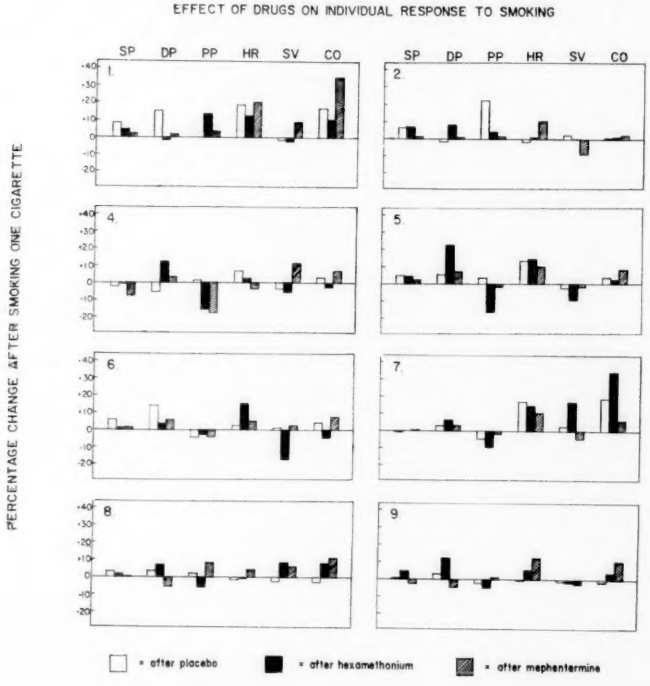

Fig. 1.—Effect of injection of a placebo and of two active pharmacologic substances on the individual response to smoking in 8 healthy young men. Each bar represents the mean of 2 tests. In the drug tests, the mean of the tests with the two highest dosage levels for that subject was used (Table I). The change after smoking is expressed as a percentage of the measurement after the injection.

stance, the resulting smoking patterns differ from one individual to another as much as the patterns after the placebo did. For this reason the usefulness of pooled data is severely limited. Nevertheless, we have looked at the data from the viewpoint of the group as a whole as well as of the individual.

Effect of Smoking After the Administration of Hexamethonium.—Eight subjects were given hexamethonium chloride at one or more dosage levels varying from 3 to 15 mg. Differences in tolerance to the drug were encountered. For example, Subject 7 became dizzy and faint on sitting up after the initial injection of 5 mg., so that the dosage was reduced on the two subsequent tests. Subject 5 had

mild symptoms after his first test at 5 mg. and more marked symptoms of faintness on standing on a very hot day after his second test at the same low dose. Subjects 1 and 2 had well marked reactions to doses of 10 and 15 mg. respectively, while Subject 6 had no reactions to doses of 10 mg. and the twins, Subjects 8 and 9, had none to 12.5 mg.

The alterations in individual responses to smoking after the administration of hexamethonium are shown in Fig. 1. Here the changes in the measurements following smoking after administration of the two larger doses for each individual have been averaged and recorded as a percentage of the post injection values. Comparison of these percentages with those obtained after injection of the placebo reveals that in many instances the differences are not striking. However, some definite changes in individual patterns were noted which were not very consistent from subject to subject. For example, in Subject 6 the response to smoking was markedly altered following the injection of hexamethonium. Whereas the mean of the placebo tests showed a moderate rise in systolic pressure and diastolic pressure after smoking, with little change in heart rate, stroke volume, or cardiac output, after the administration of hexamethonium smoking produced little change in blood pressure but a moderate rise in heart rate accompanied by a large fall in stroke volume, resulting in a decrease in cardiac output. In Subject 2, on the other hand, hexamethonium produced very little effect on the circulatory response to smoking save for a moderate rise in diastolic pressure with a consequent decrease in pulse pressure.

All 8 subjects receiving hexamethonium had one test in which a dose of 5 mg. was injected. Five minutes after the injection of this amall dose, there was a significant increase in heart rate ($p < .05$), stroke volume ($p < .025$), and cardiac output ($p < .001$), but no significant change in systolic pressure, diastolic pressure, or pulse pressure. However, comparison of the response to smoking itself after 5 mg. dose of hexamethonium with that following the placebo by the method of paired differences revealed that there was no significant change in any of the 6 variables under consideration.

When all of the hexamethonium tests for each individual are pooled and the dosages averaged, the mean dose was from 3.7 to 10.0 mg. The post-hexamethonium increases in heart rate and cardiac output noted after 5 mg. have been heightened at the larger average dosage level, while the increase in stroke volume has become smaller and is no longer significant. There was a significant mean increase in heart rate and cardiac output after the injection of hexamethonium but blood pressure and stroke volume were relatively little affected. Again no significant difference was observed in the mean changes after smoking after hexamethonium in any of the 6 variables.

Effect of Smoking After the Administration of Mephentermine Sulfate.—All 9 subjects received mephentermine sulfate at one or more dosage levels. No important reactions to the drug were encountered, although mild side effects such as feeling "wide awake," "warm," "light-headed," or "peculiar" were sometimes mentioned.

Fig. 1 shows the effect of mephentermine on the individual response to smoking. All but one subject showed a greater increase in cardiac output following mephentermine than after either the placebo or hexamethonium.

Each subject was tested at the 10 mg. dosage level. The systolic pressure, diastolic pressure, and pulse pressure were all significantly increased by the drug itself ($p < .001$, $p < .025$, and $p < .025$, respectively). After smoking the rise in systolic pressure was significantly less than in the placebo tests ($p < .01$). The heart rate was unchanged either by mephentermine or by smoking. Stroke volume and cardiac output were not affected by the drug, but after the injection of 10 mg. of mephentermine both mean stroke volume and cardiac output were significantly increased after smoking compared with the placebo test.

The data on all the mephentermine tests per individual were pooled, as was done in the case of hexamethonium, and analyzed in a similar fashion. The mean dosage for the nine subjects ranged from 7.5 mg. to 15.0 mg. Again, the drug itself produced a significant rise in systolic and diastolic pressure. After smoking, systolic pressure rose little or actually fell in some instances (Fig. 1). The mean rise in systolic pressure was significantly smaller when smoking was preceded by mephentermine compared with the placebo. Also, there was a significant mean increase in cardiac output after smoking amounting to 0.4 liters per minute. Thus, unlike hexamethonium, small doses of mephentermine sulfate definitely changed the circulatory response to smoking in normal subjects.

The Ceiling Phenomenon.—In a previous report, our observations suggested that the final figures reached immediately after smoking were much the same in a given individual whatever the initial control reading. The latter varied somewhat according to the time of day and according to whether the subject was fasting or nonfasting. We have therefore looked in the present experiment for evidence of such a smoking test "ceiling" which would be manifested by similar final readings whatever substance had been injected beforehand. The means of the final readings in the tests grouped according to the substance injected were accordingly compared by carrying out *t* tests on the paired differences. It appears that the idea of a "ceiling" does apply to a certain extent in regard to diastolic pressure and cardiac output. Thus, the mean cardiac output was significantly larger after the injection of hexamethonium than after the placebo injection, yet the mean final figures for those measurements were not significantly different. Similarly, a significant mean diastolic increase followed injection of mephentermine, whereas the final figures after smoking are quite similar to those observed after the placebo. In the case of stroke volume and heart rate, mephentermine did not significantly alter the control values, and the post-smoking values were essentially the same. The other variables did not appear to show this ceiling phenomenon after mephentermine.

DISCUSSION

In a previous study, we found that blood pressure, heart rate, and stroke volume in a group of male medical students were lower before breakfast than before lunch but showed a complementary increase in the response to smoking so that the actual readings after smoking ("the final figures") were similar.[2] This suggested to us that each subject has a "ceiling" towards which the effects of smoking tend to be buffered. This may represent a special instance of cardiovascular homeostasis, and in this study we have tried to learn something of the mechanism involved and to test its stability.

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As a first step, it would be helpful to know the means by which smoking alters cardiovascular function, but as yet this is only partly understood. One of the most important factors, nicotine, has been quantitatively studied by Gruhzit.[7] Using cats and dogs anesthetized with chloralose, he showed that there is a definite order of physiologic effects which may be demonstrated with increasing dosage. The smallest effective dose (0.125 − 1.0 μg/Kg.) produced stimulation of the aortic and carotid bodies only; slightly larger doses of nicotine (1.0 − 4.0 μg/Kg.) were required to stimulate the pulmonary, respiratory, and cardiovascular depressor chemoreflexes and the coronary chemoreflex; much larger doses (approximately 16 times the smallest effective dose) were required to stimulate the sympathetic ganglia or adrenal cortex, while stimulation of the parasympathetic ganglia was observed only when the dose of nicotine was approximately 128 times the smallest effective dose. Since a standard smoking test involves inhaling smoke from a single cigarette, the subject is exposed to a relatively small dose of nicotine. If the responses of the human being are similar to those in dogs and cats, the altered circulatory patterns after smoking may chiefly reflect changes in the state of excitability of the aortic depressor and carotid sinus mechanisms and the coronary chemoreflexes; the sympathetic ganglia, adrenal cortex, and parasympathetic ganglia would not be affected.

In the study of the physiology of the autonomic nervous system pentomethonium and hexamethonium and similar quaternary ganglioplegic drugs have proved of great value since they produce no effects which are not attributable to action on the autonomic ganglia. The effects of these drugs vary but we have noted during titration experiments that the tendency to a fall in blood pressure is often offset, when small doses are used, by a rise in heart rate which may be compensatory or may represent blocking of vagal tone.[8] Small doses producing little obvious change may cause exaggerated responses to challenges such as loss of half a pint of blood, a hot bath, or a heavy meal, which are ordinarily easily met by cardiovascular homeostatic mechanisms. It seems then that cardiovascular reflexes are impaired at a stage at which direct effects on the blood pressure or heart rate are not apparent. Accordingly, in this study we have used only small doses of hexamethonium.

Mephentermine is a sympathomimetic drug, N-methyl-ω-phenyl-tertiary-butylamine. It is a powerful pressor agent which causes bradycardia thought to be reflex, since tachycardia develops in dogs which have been previously vagotomized.[9,10] Welch and his associates find little evidence of change in the total vascular resistance when, by special experiment, peripheral flow is kept constant; they conclude that the rise in blood pressure is due to change in myocardial contractility. The maximum therapeutic effect is produced in an adult by a 20 to 40 mg. dose.[11] It appears from the study of 800 patients subjected to spinal anesthesia carried out by Blundell, Pillion, and Ansbro[12] that intravenous mephentermine acts fully for 25 minutes or more in over 90 per cent of subjects.

In this experiment we have used mephentermine in suboptimal doses to raise the blood pressure and the cardiac output a little, thus simulating pharmacologically the changes which we know occur spontaneously between breakfast

and lunch.[2] It is of interest that there was no significant mean change in heart rate after the injection was given, in spite of a highly significant rise in blood pressure.

No significant mean alteration in smoking response was found in respect to any variable after the injection of hexamethonium. The heart rate was further (though not significantly) increased and this might have been expected since both hexamethonium and smoking independently tend to increase the heart rate. Though hexamethonium acts only on the autonomic ganglia and therefore distally to the main site of small doses of nicotine (if Gruhzit's data are applicable to man) it seems to have exerted little blocking action. This may be due to smallness of dosage, or it may indicate that nicotine (or some other active principle in cigarette smoke) competes at the ganglia or acts distally. Even small doses of hexamethonium, however, are evidently able to upset the homeostatic mechanisms, since the "ceiling" is abolished for four of the six variables.

Mephentermine sulfate, on the other hand, did alter the cardiovascular response to smoking. The changes in systolic pressure and cardiac output after smoking were significantly affected by the previous injection of the drug. With this drug, too, the "ceiling" is changed, but it is of interest that on the average the initial effect of the drug is offset to some extent by the response to smoking so that there is less of a discrepancy between the final figures than there is in those after the injection. We interpret this as a tendency toward the "ceiling effect."

In conclusion it appears that this experimental approach reveals individual differences in homeostasis, but that these changes are not readily grouped. At present the results seem too various and too complex to permit a simple classification of subjects, based on reaction patterns following such tests, which could be used for screening purposes.

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SUMMARY

Observations were made on the circulatory response to smoking a single cigarette following small intravenous injections of hexamethonium, of mephentermine, or of placebo (isotonic sodium chloride solution). These substances were given in random order in a series of separate double blind tests.

Seven healthy white male subjects had 8 tests apiece on different days, 3 with each of the active pharmacological preparations and 2 with the placebo. Two other subjects had smaller numbers of tests.

The aim was to produce minimal measurable effects, and since sensitivity varies from subject to subject, the appropriate dose had to be found by experiment.

After injection of the placebo, the average circulatory response to smoking one cigarette was similar to that in a larger series previously reported, in which no injection was given. From the duplicate placebo tests an estimate of the average variability of these tests could be made.

Hexamethonium did not influence the mean response to smoking so far as could be judged by a paired comparison with the placebo tests. Individual differences were noted, but it is difficult to assess their importance.

When the mephentermine sulfate and placebo tests were compared, both the change in systolic pressure and in cardiac output after smoking were significantly altered by mephentermine. The other variables were not thus affected.

The constancy within the individual of the measurements obtained after a cigarette is smoked, previously reported as the "ceiling phenomenon," is impaired but not entirely abolished by small doses of these drugs. In this respect the "ceiling phenomenon" resembles a cardiovascular homeostatic mechanism.

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FAMILY STRUCTURE IN RELATION TO HEALTH AND DISEASE
A Review of the Literature

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THE relationship between family structure and disease is a subject of increasing interest as the concept of psychosocial factors in the etiology of disease broadens. The focus of this report is on simple easily measured aspects of the family, and on the ways in which they appear to relate to psychosomatic and mental diseases and to certain aspects of health. The data reviewed have been subdivided into five categories for presentation: parental deprivation, sibship size, position in the sibship, marital status, and number of children. First the literature on each variable will be presented along with a discussion of the problems of competent measurement. Then the possible usefulness of each variable and its value for future research will be considered.

This review is very largely limited to reports written in English and dealing with the situation in western culture. Since the focus is on better understanding of disease, no attempt has been made to cover the obvious effects of disease on family structure. Because of the difficulties of analyzing incomplete families, certain diseases of early life on which there is some intriguing data such as rheumatic fever, leukemia, coeliac disease, and nephrosis have been excluded. Furthermore, malignant disease and infectious disease, except for tuberculosis, have been categorically excluded. Finally, those studies where the basic numerical data were not presented and those studies that deal with less than 25 persons have, in general, been omitted.

PARENTAL DEPRIVATION

The bulk of the numerical data from the literature on parental deprivation is summarized in Fig. 1. On the second line of this figure is presented some data on various population groups. The first of these studies, giving an estimate of

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15 per cent parental deprivation before age 16, is a study of a segment of the nonfaculty employees of a University.[1] The sample is fairly small and can hardly be considered representative of the community in which the university is located. It is our belief that this is below the true average for the general population. The next estimate of 17 per cent is derived from a household survey in the Arsenal Health District of Pittsburgh,[2] and represents an actual count of children age 15 to 17 who were not living with their natural parents. As an estimate for the general population, this is also probably low because it did not include children in orphanages or similar institutions, and because there may have been moderate under reporting of stepchildren, since no special efforts were made to identify them.

The next 2 estimates are based on data of the Metropolitan Life Insurance Company, collected respectively in 1953[3] and 1940,[4] relative to the number of children having lost a parent by death before age 18. This information has been adjusted to include divorce and separation on the basis of the data cited by Wahl[5] that approximately one-third of the total number of parental deprivations among the Bainbridge recruits in the Navy were due to divorce or separation. Finally, the last figure is based on Wahl's report on Navy recruits in 1953-54. This is probably high for several reasons. First, the data are reported in such a way that those recruits who lost both parents by death might be counted twice. Second, all recruits are included irrespective of age, resulting in a median age of 19 years. Third, no statement is made about the proportion of these men who were volunteers for military service. If there were substantial numbers of volunteers in the group, it can hardly be looked on as a random sample of the population.

With all the problems in mind, we are inclined to estimate that 20 per cent is a reasonable reference point for the proportion of American young people now losing one or both parents by death, divorce, or separation before age 16. This is substantially above the figure for the University faculty[1] on the first line and suggests that further information about individuals successful in various pursuits would be interesting.

On the third line are several "control groups." Three of these have quite high proportions of parental deprivation but when one realizes that one of them is a sample of state mental hospital employees,[7] and another is a group of patients from a general hospital,[9] one is not so surprised at the distribution.

Moving down the figure, the next thing one notices is that all the other groups have percentages of broken homes that exceed the 20 per cent which is the estimate for the general population groups discussed above. It should be noted that some of the groups are rather ill defined such as "psychiatric patients"[18] and persons with miscellaneous "psychosomatic diseases."[33] They are included only to show that striking deviations from the rest of the population are not confined to certain narrow diagnostic categories. On the other hand, there are 3 specific diagnostic categories that stand out from all the rest as having the highest average per cent with broken homes. Tuberculosis patients[20] and accident repeaters[19] appear to report parental deprivation two to three times as often as the general population of the United States, and persons attempting suicide report it more than three times as often.

Related findings from an entirely different kind of study are reported by Spitz[38-40] who studied children raised under two different circumstances. The first group was composed of foundling children cared for after the third month by the regular nursing staff of the institution, while the second group was made up of children raised by their natural mothers who were wayward girls sent to the institution. These two groups were compared and it was found that while the group cared for by their mothers was healthy and developed normally, the children reared by the busy nursing staff were retarded in their development and had a 37 per cent mortality in the 2 years of observation. These differences

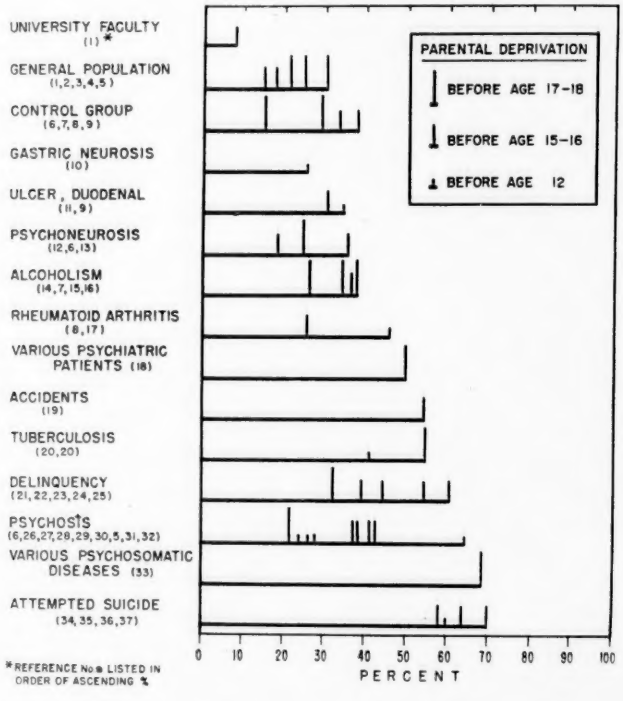

Fig. 1.—Parental deprivation due to death, separation, or divorce for normal persons and persons with certain disease categories before or by the age of 18.

occurred despite the fact that the general environment, including the food, sanitation, and medical care were identical for the two groups. However, it should be recognized that new infections were presumably being introduced regularly into the nursery by the newcomers. To these the infants cared for by their mothers were not exposed. Similar findings with regard to early parental deprivation are reported by many authors.[41-49] These reports suggest that retarded physical, mental, and emotional development, deviant behavior, and certain diseases are found among those who have been deprived of parental care, especially that of the mother, early in life.

In proceeding to evaluate the significance of the above findings, we must consider the definitions of a broken home, the age up to which the deprivation of a parent is considered significant, the time of the study, and the type of data that is most useful. First, parental deprivation may include parental death, divorce, separation, sickness, neglect, or rejection according to the views of the author concerned. The studies presented in Fig. 1 refer only to death, divorce, or separation.

The second important point is that authors vary in their opinions with regard to the age up to which a parental loss is considered to be important. As noted on the figure, the studies reviewed have been grouped and separately identified as those in which the period of interest extended only up to age 12, those in which the period was continued through age 16, and finally those in which a loss through age 18 was considered relevant. It is most important to keep these distinctions in mind, for there is at least a 50 per cent greater probability of a broken home occurring in an 18-year period than in a 12-year period.

Third, the probability of a home being broken by a parental death before the child is 16 has decreased sharply in the last 50 years due to the increasing expectation of life.[50] On the other hand, divorce rates have fluctuated but show a tendency to increase. It is, therefore, important to make sure that comparative studies relate to the same epoch. With regard to the material presented in Fig. 1, three-fourths of it was published since 1950. Only four of the papers were published prior to 1940; and the earliest was published in 1934. It can then be said that we are dealing with the same general epoch, though some of the differences may be accounted for by the dates when the studies were made and by the ages of the persons studied.

Fourth, parental deprivation is more common in the lower social classes where general mortality is higher.[49a] Since some of these conditions are thought to be more common in the lower social classes (tuberculosis,[20] arthritis,[17] juvenile delinquency,[22-24] schizophrenia[32a,b]) a possibility of a spurious correlation exists here. On the other hand, for psychoneurosis,[32a,b] which is alleged to be more frequent in the upper social classes, it is possible that a stronger association exists than is shown here. Unfortunately, none of these studies were controlled for social class. It is important that this be done in future research on this subject.

Finally, there are at least three ways to approach a study of the relationship between parental deprivation and disease. One can study the incidence of disease, i.e. the number of new cases per unit of population per unit of time, in those who are orphaned and those who are not, or one can study the prevalence of disease, i.e. the number of cases of disease per unit of population that exist at a given point in time, or one can examine the proportion orphaned among cases and controls. Incidence studies are clearly the most valuable, for they give direct estimates of the relative risk of developing disease in the groups of interest. Prevalence studies are less valuable, for the duration of the disease has an influence on this parameter. Finally, the examination of the proportion orphaned among cases and controls offers no direct estimate of relative risk though, as will be shown below, under certain assumptions the relative risks can be approximated. It is unfortunate that most of the data available are of this nature

and in many instances no controls were studied. However, when these are all assembled as in Fig. 1, very definite impressions are gained about the frequency of parental deprivations in various diseases as compared with the general United States experience.

Employing the method of Cornfield[51] one can go further than this, if one is willing to assume that the cases in hand are a random sample of all cases of the condition. For example, the computations suggest that the relative risk of attempted suicide, of accidental injury, and of having tuberculosis are respectively seven, five, and four times as great for those who have been orphaned as for those who were reared in an intact family. Clearly, there is a great need to study the medical problems of orphans.

The importance of parental deprivation probably lies in its emotional significance for the individual. On the one hand, it is quite possible for an orphan to function effectively, as is indicated by the fact that ten of the American Presidents[52-56] lost one or both parents before the age of 16. On the other hand, two studies[18,57] have indicated that divorce and separation are relatively more dangerous to the offspring's healthy development than death. Furthermore, Nye[58] and Lidz[59] have suggested that it is really the "unhappy" home, not the "broken home" per se, that should be studied in association with ill health. It has been found,[6,13,24,60] that deprivation of proper parental care is often associated with feelings of insecurity, inferiority, anxiety, and fear. It, therefore, seems reasonable to postulate a chain of events progressing from parental loss through certain emotional states to altered physiologic function which may contribute to disease.

All of this suggests several lines of further epidemiologic research. First, there is need for direct attention to this variable in large sample surveys such as the current National Health Survey, and in smaller more intensive surveys in which clinical examinations can be performed and the home situation evaluated. Second, there is a great need for follow-up studies of the children of disrupted families. These studies should include orphans, children of divorce, and children of families in which marital strife is so great that the problem comes to the attention of an agency even though a divorce does not result. Finally, more field experiments should be performed to see if some of these unfortunate results can be prevented by various methods of handling the children in question. Such studies are expensive and time consuming, but will be important from a public health point of view because they relate to a group of people who seem to have increased probabilities of developing psychiatric and psychosomatic disease.

SIBSHIP SIZE

The literature on sibship size is full of conflicting and dubious evidence. For example, some authors have reported that scientists[61] and geniuses[62,63] tend to come from large families, while others[64,65] report that they come from small families. It has been suggested that juvenile delinquents,[25,66] mental defectives,[67] criminals,[68] psychotics,[5,6,31] psychoneurotics,[6] and rheumatoid arthritics[69,70] tend to come from large sibships, whereas obese children[71,72] are thought to come from small families.

In proceeding to evaluate such statements concerning the association of sibship size with intellectual attainment and disease, it is necessary to look at the sampling methods and at the problem of spurious correlations. With regard to sampling method, the most important thing is to check that the sampling procedure is the same for the cases and controls. It is, for example, wholly inappropriate to compare the distribution of family sizes among patients with the distribution reported in a census, or other enumeration where families constitute the basic unit for counting. The reason for this is evident on consideration of an hypothetical population consisting of equal numbers of families with one child and ten children. If one picks families and asks how many children there are, one has an equal chance of picking large families or small families and concludes that the average size is 5.5 children. If, on the other hand, one picks individuals and asks them how many siblings they have, the probability of picking a person from a large family is ten times as great as the probability of picking a person from a small family. In this situation, one would conclude that average size of a family is 9.2 children. The mathematics of all this were conveniently summarized by Karl Pearson[73] and effectively applied by Gregory.[74] Unfortunately, some authors have neglected this principle and have falsely concluded that their patient groups came from unusually large families.

The soundest way to approach this entire problem is, of course, to examine attack rates of disease by size of sibship, but this can only be undertaken when a survey of a total population or sample of the population has been conducted. Material from the Pittsburgh Arthritis Study[8] may be used as an illustration of this principle. The data drawn from this study indicate that the prevalence rate for the index of rheumatoid arthritis[75] among persons from sibship size 1 or 2 is 3.6; from sibship size 3 or 4, it is 6.6; from sibship size 5 or 6, it is 7.8; and from sibship size 7 or greater, it is 10.1. These data show an association between family size and rheumatoid arthritis, which, as will be indicated below, may be merely a function of social class.

With regard to the problem of spurious correlation with sibship size, it should be noted that this variable is clearly related to date of birth,[76,79] social class,[77-79] and cultural orientation.[78,80,81] In Fig. 2 is demonstrated the nature of the general trend of sibship size in the United States in relation to date of birth. The various sources of data are all based on sampling individuals rather than families, therefore, the graph is comparable to data that might be obtained from patient groups. The lowest line is an average of the information that we have extracted from historical sources[54,56] on the American Presidents, with the information provided by Yoder[82] on a group of internationally eminent men. The second curve is derived from our analysis of the geneaology of about 9,000 families descended from John Whitney,[83] who came to this country in 1635.

Finally, the third curve is a composite of data from the 1940 census[84] plus a segment of the nonfaculty employees in a University.[1] This last was added to give an impression of the most recent trend even though the numbers are so small as to give little stability to individual points. It might be fun to speculate as to the reasons for the different shapes of these curves, however, since they are probably related to some of the factors to be discussed below, we will merely note that since about 1800 there has been a general downward trend in sibship size.

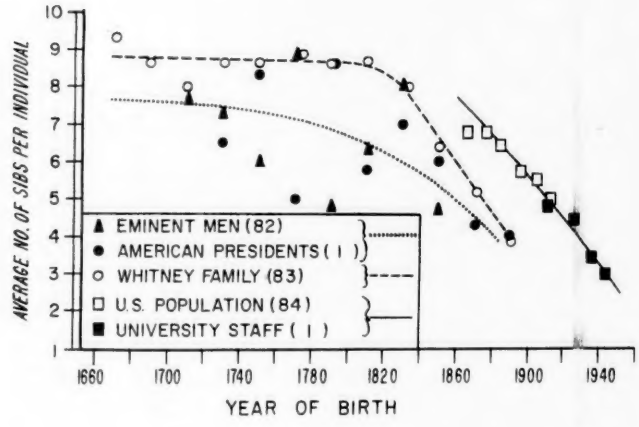

Fig. 2.—Mean size of sibship per individual at different periods, for specified groups.

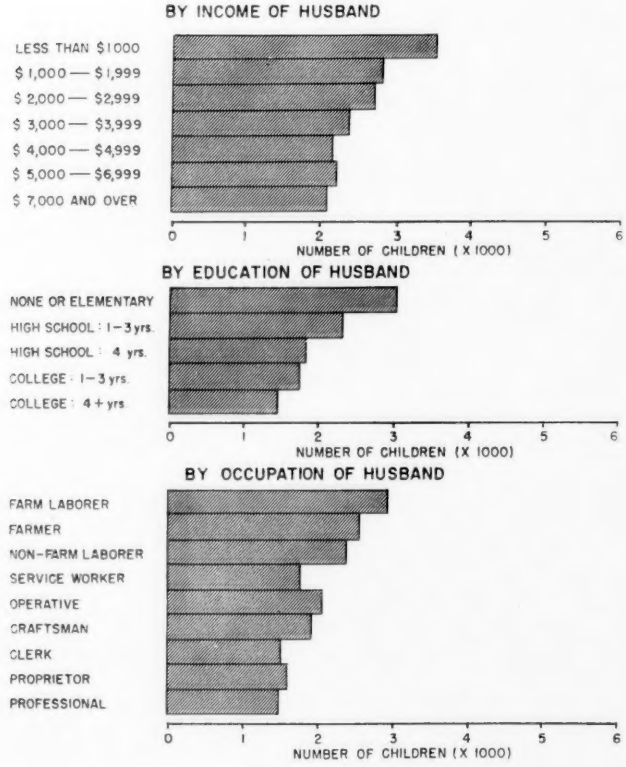

Fig. 3.—Number of children ever born per 1,000 ever married white women, age 45 or older,[78] by status of husband.

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In Fig. 3, the effect of income, education, and occupation on size of family is depicted. These are the principal variables ordinarily used in determining social class, and it is quite clear that they are closely associated with family size. Fig. 4 illustrates that there are quite striking differences by race, by place of residence, and by country of birth of the mother. Finally, the interaction of place of residence and education is nicely demonstrated in Fig. 5. These figures indicate the importance of a control on multiple variables if one is going to study the problem of family size in connection with health and disease.

Studies to date have not demonstrated clear-cut relationships between sibship size and disease. Part of the reason for this is that the complexities of the interrelated variables such as date of birth, social class, religion, and cultural orientation have usually been neglected or poorly controlled. It seems unlikely that much increase in our understanding of psychosomatic disease processes will be gained from the study of their relationship with family size unless very large scale studies, in which these variables can be controlled, are undertaken. Perhaps this is just as well, for Bossard[85] has suggested that really it is the nature of the infrafamilial relationships rather than the size of the sibship that is important.

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POSITION IN THE SIBSHIP

The relationship of position in the sibship to various aspects of health and disease has been a subject of discussion for nearly 100 years. In 1866 Mitchell[86] published his observations on the excess frequency of idiocy in the first born, but 11 years later Galton[61] did a study on English men of science, pointing out that there was a considerable excess of first born children in this group. Since that time, there has been scattered interest in this aspect of family structure in relationship to longevity,[87] intelligence,[88-94] achievement,[82,95-97] personality traits,[98-102,104] and certain diseases.[71,72,103,105-112]

The methodologic problems related to this kind of study have been hotly debated by many competent people. The most admirable treatment of methods for this problem is to be found in Gregory's paper[74] which should be consulted by all persons intending to investigate a patient group with regard to this variable. At risk of seeming repetitive, it should be emphasized at this point that in the long run there is no substitute for adequate studies of the annual incidence rate of disease in the various relevant categories of ordinal position. However, since incidence rates for most of the diseases in which we are interested are extremely difficult to come by, we often have to settle for prevalence studies. This latter, of course, requires a population survey and the data can be presented as is done in Table I for rheumatoid arthritis and obesity in the Arsenal Health District of Pittsburgh.[113] Sometimes we get rather odd, though still very useful, data like that presented by Rivers[110] from which one can calculate that in a group of families where one sibling had tuberculosis the proportion of persons ever known to have developed clinical tuberculosis is 30 per cent for the first born and 20 per cent for those of other birth ranks. These data do not exclude the "only" children, but do give some impressions of the added susceptibility of the first born to tuberculosis.

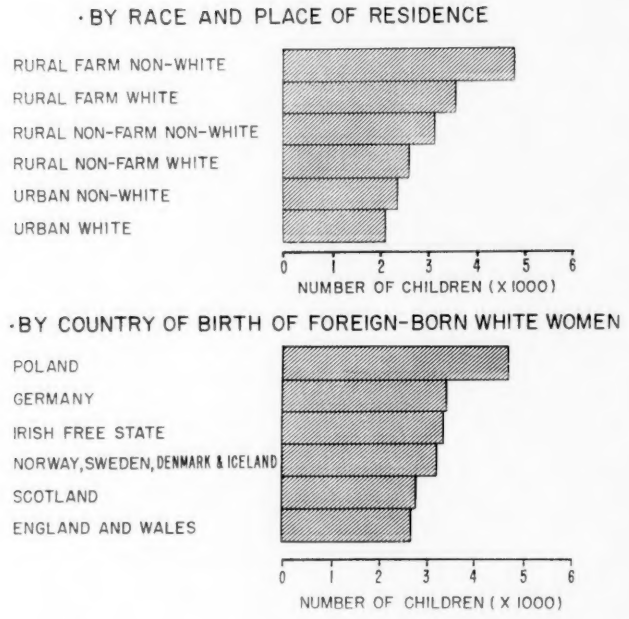

Fig. 4.—Number of children ever born per 1,000 ever married white woman, age 45 or older,[78] by race and location.

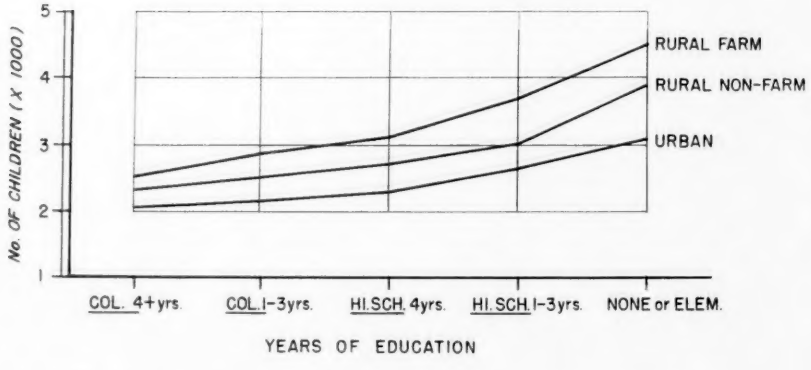

Fig. 5.—Number of children ever born per 1,000 ever married white women, age 45 or older,[78] by status of wife.

Gregory[74] has pointed out that in any population sample from which "only" children are excluded, the ratio of the number of eldest to the number of youngest children should be precisely one, subject only to sampling variation. This is because each sibship of size two or greater has both an eldest and a youngest child. Curiously enough, very little use has been made of this rather obvious fact. In Table II is presented information on the percentage distribution by

ordinal position along with the eldest-to-youngest ratio for various groups of people. In the first section of this table, items 1 though 3, it is shown that randomly selected groups of persons turn out to have the expected eldest-to-youngest ratios of 1.0. However, in the samples of hospital patients, items 4 through 6, some variation appears which may be related to factors influencing admission to the hospital and/or the diagnosis for which the patients were selected. It is not clear why Sletto's[115] controls, the normal high school students in item 7, deviate from the expected value, but a selection bias is suspected as the reason for this deviation.

From the second section of this table, items 8 through 12, it is clear that persons of recognized intellectual attainment tend to be drawn from among the eldest children. In contrast to this is information about fighter pilots presented by Schachter[126] which suggests a dearth of eldest sons among the aces (those who shot down 5 or more enemy planes during a tour of duty in Korea). Unfortunately, Schachter has not separated the youngest from those of intermediate position, so we cannot compute an eldest-to-youngest ratio; however, the implication is that this ratio is likely to be low. In a similar vein we obtained family information on 15 professional baseball players and were struck by the fact that 8 of them were youngest and none were eldest. Such a distribution would occur only once in 256 samples on a purely chance basis. This difference in eldest-to-youngest ratio, with those of intellectual prowess high and those of physical prowess presumably, low certainly warrants further investigation.

TABLE I. AGE AND SEX ADJUSTED PREVALENCE RATES PER 100 FOR RHEUMATOID ARTHRITIS AND OBESITY BY POSITION IN THE SIBSHIP. ARSENAL HEALTH DISTRICT OF PITTSBURGH, 1953 TO 1955

DISEASE	ONLY	ELDEST	INTERMEDIATE	YOUNGEST
Rheumatoid arthritis*		5.1	4.7	6.7
Obesity	25.2	22.7	26.8	28.8

*Diagnosis based on two examinations, about one year apart.

The most striking thing from this table is the very high eldest-to-youngest ratios exhibited by patients with asthma, indicating that this disease is very commonly a disease of the eldest child. This seems to tie to the theoretical formulations[106,141,142] with regard to asthma, which suggest that separations and threats of separation, particularly from the mother, are of great importance in this disease. If we were to think in terms of the patient with asthma being sensitized to separation events early in life it is readily understandable why the oldest who is forced to share his mother with younger siblings might be more frequently afflicted than the youngest who is never subjected to this.

Turning now to peptic ulcer we see that low ratios are consistently observed for persons with duodenal ulcer and gastric ulcer. Since dependency-independency conflicts seem to be associated with duodenal ulcer[134-138] it is not surprising that youngest children are more commonly affected, since in the average American home they have somewhat prolonged periods of dependency. For alcoholic

TABLE II. PER CENT DISTRIBUTION BY POSITION IN SIBSHIP FOR NORMAL PERSONS, PERSONS WITH SUPERIOR ABILITY, AND PERSONS WITH CERTAIN SPECIFIED DISTURBANCES

ITEM	TYPE OF PERSON	NO.	SEX	PER CENT				RATIO: ELDEST TO YOUNGEST
				ONLY	ELDEST	INTER-MEDIATE	YOUNGEST	
1	Naval recruits[5]	100,000	M	9.0	27.0	34.0	27.0†	1.0
2	University staff[1]	156	M + F	11.5	28.8	30.8	28.8	1.0
3	Normal control in ulcer study[114]	50	M	14.0	22.0	42.0	22.0	1.0
4	Hospital patients[108]	495	M + F	9.1	25.7	44.8	20.4	1.3
5	Hospital patients[9]	250	M	4.8	21.6	48.8	24.8	0.9
6	General in-patients of hospital[12]	500	M + F	8.4	23.4	45.5	24.1	0.9
7	High school students[115]	786	M + F		22.0	52.0	26.0	0.9
8	Eminent American men[62]	261	M	3.8	28.0	54.0	14.2	2.0
9	American presidents[1]	33	M	3.0	30.3	51.5	15.2	2.0
10	English men of science[61]	99	M	22.2	26.3	36.4	15.1	1.7
11	British genius[63]	309	M + F	*	30.4	47.9	21.7	1.4
12	American scientists[116]	506	M	15.6	33.4	25.1	25.9	1.3
	Patients with:							
13	asthma[117]	45	M	24.4	37.8	24.4	13.0	2.9
14	asthma[118]	19	M + F	10.5	47.4	21.0	21.0	2.3
15	asthma[106]	375			41.1		20.1	2.0
16	asthma[106]	114			40.3		26.3	1.5
17	hypertension[119]	26	M + F	15.4	26.9	34.6	23.1	1.3
18	gastric neurosis[10]	146	M	10.0	42.0	12.0	36.0	1.2
19	neurosis[12] (Patients attending Psychiatric Dept. of Gen. Hospital)	500	M + F	9.0	19.2	46.8	25.0	0.8
20	Juvenile delinquent[115]	1,046	M + F	10.0	21.0	51.0	18.0	1.1
21	Juvenile delinquent[25]	500	M	4.8	15.6	60.0	19.6	0.8

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	Persons with:							
22	rheumatoid arthritis[70]	241	M + F	7.5	22.8	45.2	24.5	0.9
23	rheumatoid arthritis[17]	43	M + F	9.5	23.8	40.5	26.2	0.9
24	duodenal ulcer[9]	250	M	6.8	18.0	55.2	20.0	0.9
25	duodenal ulcer[114]	50	M	8.0	20.0	48.0	24.0	0.8
26	duodenal ulcer[11]	62	M	3.0	11.0	55.4	30.6	0.4
27	gastric ulcer[114]	50	M	10.0	20.0	44.0	26.0	0.8
28	peptic ulcer[120]	25	F	24.0	24.0	24.0	28.0	0.9
29	anorexia nervosa[121]	26	F	0.0	15.4	57.7	26.9	0.6
30	alcoholism[14] (Middle class)	274	M + F	12.4	31.0	38.3	18.3	1.7
31	alcoholism[123] (Workhouse)	50	M	6.0	26.0	46.0	22.0	1.2
32	alcoholism[124] (State Farm Patients)	32	M	18.8	31.2	21.9	28.1	1.1
33	alcoholism[124] (Out-patients)	90	M + F	13.3	28.9	28.9	28.9	1.0
34	alcoholism[103] (With police record)	110	M	9.1	21.8	35.5	33.6	0.6
35	alcoholism[123] (Clinic patients)	50	M	18.0	18.0	34.0	30.0	0.6
36	alcoholism[107] (Hospital patients)	230	M	6.0	17.0	47.0	30.0	0.6
37	childhood obesity[71]	61	M + F	24.6	32.8	21.3	21.3	1.5
38	childhood obesity[72]	40	M + F	30.0	25.0	8.0	37.0	0.7
39	schizophrenia[108]	442	M + F	5.2	22.2	53.8	18.8‡	1.2
40	schizophrenia[125]	75	M	6.7	18.7	36.0	9.3	1.1
41	schizophrenia[31]	227	M + F	11.0	24.0	42.0	23.0	1.0
42	schizophrenia[31a]	156	M + F		35.3	29.5	35.3	1.0
43	schizophrenia[74]	549	M + F	5.0	23.0	48.0	26.0	0.9
44	schizophrenia[5]	568	M	14.0	18.0	42.0	26.0	0.6

*Only child is excluded from analysis.
†3 per cent no information.
‡29.3 per cent no information.

groups, it is interesting to note that the one sample that comes anywhere near being representative of the general population gives a high ratio,[14] while the other samples mostly have normal[123,124] or low ratios.[103,107,123]

Two more points should be noted from Table II. The first is the excess of childhood obesity in the "only" position.[71,72] This is in line with the finding noted in the previous section that this disease is relatively frequent in small families. The second is the excess of juvenile delinquency[25,115] and anorexia nervosa[121] in the "intermediate" position. It is not safe to conclude that this is entirely due to an effect of intermediate birth order, as is suggested by some authors,[115,128] for it might equally be an effect of social class acting through family size.

There are a few studies on birth order, the results of which cannot be presented in table II because the data are not amenable to transposition into the form of that table. The first is the observation by Carman[129] confirmed by MacDonald[130] that the eldest born tends to be more sensitive to pain than the younger siblings. The second is that in a study of military inductees[127] the oldest sons were found to have on the average higher pepsinogen levels than those of intermediate position who in turn had higher levels than the youngest and only sons. This is particularly interesting in view of the fact that high pepsinogen values are associated with peptic ulcer and yet peptic ulcer, as has already been shown, is a disease found most frequently in the youngest son.

The last subject of importance is tuberculosis. Three studies[73,110,112] have shown that the first born is more likely to develop clinical tuberculosis and/or die thereof than those of lower birth order. Unfortunately, in these studies the emphasis was on ordinal position rather than relative position in the sibship. The only child was not separated from the first born and the youngest was not identified as such but merely listed in the appropriate numerical position.

There are two additional factors which are possibly worthy of study. The first is sibling space, the interval between the birth of the next older and the next younger sibling. Some attempts have been made to study this, but to date no statistically significant results have been uncovered. Similarly, studies of the sex of adjacent sibs such as the observations on anorexia nervosa[121] and psychoneurotics[122] are suggestive and worthy of further study. Other authors[131,132] have studied these two variables together. Their results indicated the interacting influence of these variables on the development of certain personality traits, such as aggressiveness, competition, curiosity, and dependency.

It seems evident that study of eldest-to-youngest ratios in diseases in which psychosocial factors are thought to play important parts may be quite useful in suggesting more specific variables for further investigation. Such studies are easily conducted, for in any intact population group, the ratio should always be one, and preliminary measurements can be made without benefit of controls unless one is dealing with a clearly atypical base population such as a group of executives.

MARITAL STATUS

Around 1940, Ciocco[143,144] called attention to the fact that when one marital partner died the second was likely to die soon. Since that time, additional evidence on mortality and morbidity by marital status has become available. The

most striking bit of information comes from the work of Shurtleff,[145] subsequently supported by studies of the Metropolitan Life Insurance Company,[146] and Krause[146a] indicating that, in general, mortality is higher among those who have remained single, or whose marriage has been terminated, than among those who are married. This is true for both sexes and is most striking in the younger age groups where larger differences can, of course, be demonstrated.

There are several categories of disease in which those who are unmarried or no longer married have very much higher mortality rates than those who are married. These are influenza and pneumonia, syphilis and cirrhosis of the liver, "violence," and tuberculosis. On inspection of these several causes of excess mortality, we get the impression that there are three major factors which seem to be operating. The first is clearly the absence of mutual care between the spouses and is exemplified by the increased number of deaths from influenza and pneumonia, which in this day and age are mostly unnecessary deaths when adequate medical care is sought in sufficient time. The second group of diseases is one in which the condition itself, or the etiological factors contributing to the condition, may lead to the celibate state. It is self-evident that alcoholism and sexual promiscuity frequently lead to the termination of marriage. Similarly, it is likely that they reduce the frequency of marriage. Therefore, it is not surprising that cirrhosis and syphilis are in excess among those who are not married. The third category is one in which social isolation may play a part and contains suicide, tuberculosis, and accidents. The proposition that social isolation may be related to these conditions will be discussed below. Whether hypertension and vascular lesions of the central nervous system should be included in this group is not clear, but they are particularly frequent among the young widowed.

Before leaving mortality data entirely, it is appropriate to direct attention to a situation in which case fatality rates seem to be related to marital status. Schmid[147] has noted that the suicide case fatality rate, i.e., the percent of attempted suicides ending fatally, is 9 per cent for single women, 16 per cent for married and separated women, 20 per cent for divorced women, and 37 per cent for widows. Somewhat similar data are presented for males but are not so striking. Unfortunately, these are not age adjusted, so we cannot be sure that a goodly portion of the variation is not due to age.

Turning next to the available data on morbidity, we find relatively less useful information. In Table III is presented a sample of the kind of information that is available in the literature. Though potentially very interesting, these data are of little value as evidence for they have not even been adjusted for age. However, they suggest further investigation and remind us of the well known facts that persons with schizophrenia tend to avoid marriage[125,149] while persons who are alcoholics are often repeatedly married and divorced.[150-152]

Again with respect to marital status it is necessary to have age specific or age adjusted incidence or prevalence rates of the diseases under study for each of the several categories. We have unhappily been unable to find any such rates for diseases other than myocardial infarction. Certainly Biörck[153] should be congratulated for presenting the first really sound data on this subject, even

though the differences he finds are not striking. From the data presented by Wolff[154] on industrial accident proneness one can reconstruct the fourfold table for the relationship between accident proneness and marital status, and show that the prevalence of persons who had 10 or more accidents per year is 20 per cent for the unmarried and marriage terminated, as compared with 4 per cent for the married. The differences between these figures may be exaggerated by a difference in age distribution between the married and those not currently married. Specifically, the accident rate is higher among the younger employees who are most apt to be single, but it is our impression that this can account for only a small part of the fivefold difference in prevalence of persons with 10 or more accidents per year.

TABLE III. PER CENT DISTRIBUTION OF PERSONS OF MARITAL STATUS—SPECIFIED DISEASES COMPARED WITH THE U. S. POPULATION

	SINGLE	MARRIED	MARRIAGE TERMINATED	TOTAL
U. S. population[118]	23	67	10	100
Attempted suicide[34]	29	45	26	100
Tuberculosis[20]	33	46	21	100
Duodenal ulcer[11]	34	55	11	100

Some data on rheumatoid arthritis and obesity from our studies in the Arsenal Health District of Pittsburgh are presented in Table IV. The arthritis data support an earlier finding from a smaller study in which actual diagnoses of rheumatoid arthritis were made,[156] and is supported further by a study of persons in the process of getting a divorce[157] which reveals that rheumatoid arthritis and divorce are associated. All 3 of these studies show that the association is stronger for males than for females. With regard to obesity, it is interesting to note, that Shurtleff's[145] hypothesis that married women might be more obese than those who remain single is not borne out.

TABLE IV. AGE-ADJUSTED PREVALENCE RATES PER 100 FOR AN INDEX OF RHEUMATOID ARTHRITIS AND AN INDEX OF OBESITY BY MARITAL STATUS AND SEX

	RATES PER 100 PERSONS					
	MALES			FEMALES		
	SINGLE	MARRIED	MARR. TERM.	SINGLE	MARRIED	MARR. TERM.
Positive index of rheumatoid arthritis[155]	0.9	2.9	27.3	7.6	7.4	7.6
20 per cent or more above average weight for specified height at age 25[113]	23.9	23.4	31.4	31.9	25.8	41.8

It is quite apparent that we need more adequate epidemiologic data in this area. Though it is possible to get some crude preliminary estimates as to the value of further investigation of variables of this nature by simply taking percentile distributions by marital status among persons found to have the disease and comparing them directly with percentile distributions of persons in the general population, this procedure suffers from the very real difficulty that each disease has its own particular age distribution which may be very different from the age distribution of the general population. It is, of course, possible to take age-specific rates for various marital states and apply them to the appropriate age groups of the patient population and get an expected value for the distribution by marital status, according to the method used by Doll and Hill[158,159] in their studies of malignant disease. This method still suffers from the fact that patient groups are selected for many things other than their disease. If they are clinic patients, they tend to come from lower socioeconomic groups. If they are hospital patients, there are special factors associated with their hospitalization which may or may not be related to the severity of their basic disease process. Therefore, the best way to approach this problem seems to be in the study of entire populations, where incidence and/or prevalence rates can be used to indicate the frequency of disease in each marital status group.

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NUMBER OF CHILDREN

There are 3 recent observations with regard to the relationship between number of children and disease which we cannot omit, though we find it difficult to interpret them. First, Burger[159a] has shown a direct linear relationship between the frequency of peptic ulcer and number of children for a group of employed men. Second, it has been pointed out by Miall[159b] that blood pressures are higher among the childless, be they men or women, and that in general the greater the number of children the lower the pressure. Furthermore, in a 4 year interval these men and women who added to their families had on the average smaller rises in pressure than those who did not.[159c] For women King[155] has demonstrated a positive association between rheumatoid arthritis and large numbers of children. All of these observations appear to be independent of age.

In thinking about these associations we do not immediately fit them into thoroughly satisfactory places in relation to our other knowledge of the several diseases. This is particularly true of the hypertension story which is by all odds the hardest fact of the three. It is, of course, important to remember that if there is a causal chain it may run from the family size to the disease or from the disease to the family size. However, we must never forget that there may be no casual chain at all. If eventually this should prove to be the case, the information is still likely to be useful is building a better understanding of these diseases, for it may lead us to other more meaningful associations.

DISCUSSION

In each section, we have tried to emphasize the importance of sound methodology in approaching this kind of problem. Repeated attention has been given to the need for field studies from which incidence or prevalence figures could be

obtained. Such studies will have to be done on large samples and so will be expensive. It would seem better, therefore, to build inquiries with regard to family structure into ongoing field studies with respect to specific diseases. It also seems possible that organizations such as the National Health Survey might be able to gather some useful data in this area. When field studies are not possible, studies of patients compared with controls are certainly useful. However, one must be extremely wary in designing such studies lest one fall into the pit of using improper controls, and hence be led to faulty conclusions.

No claim has been made that the variables here discussed are basic in their relation to health and disease. This is important because the demonstration of association between two variables is quite different from the demonstration that one is necessary and/or sufficient for the other. Since the associations reviewed here may not be casual, in what way can they be useful? First, they may be useful as predictors of increased risk. For example, we have seen from the first section that orphans are unduly liable to certain conditions, particularly suicide, tuberculosis, and accidents. This means that orphans as a group are worthy of special attention in public health thinking, and when an orphan is being cared for by a physician these problems should be given special consideration.

The second way that these associations may prove useful is in suggesting lines of thought for development of specific hypotheses. Let us consider for a moment tuberculosis, accidental injuries, and suicide. As shown above, these conditions are associated with parental deprivation and termination of marriage. For suicide, this information fits very well into the hypothesis that social isolation, i,e., reduction of those social contacts and relationships which are of personal significance to the individual, is an important factor. This notion was advanced first by Durkheim[160] and was supported later by Miner[161] and Sainsbury.[162] Could such an hypothesis be applicable also to tuberculosis, and accidents?

Since this similarity of family pattern suggests that tuberculosis might also be a disease to which social isolation is relevant, other evidence on this point has been sought. In the first place, Hawkins[163] and Bräutigam[163a] have called attention to the fact that stressful events, particularly those involving some element of separation, such as bereavement, loss of job, move to a new community, change in sociability, and financial stress are frequently associated with the onset of clinical tuberculosis. Turning to more specific situations in which isolation is obvious, one thinks immediately of jails, and there is ample evidence that tuberculosis rates are excessive among the inmates of our prisons.[164-166] By the same token, there is evidence that tuberculosis rates are also excessive in mental hospitals. Admittedly, Katz[167] and his colleagues have tried to demonstrate that the excess of tuberculosis in mental hospitals might be due partly to age distribution, socioeconomic group from which the patients come, and greater opportunity for infection within the hospital, but primarily to coexisting organic disease. They fall a bit short of a satisfactory explanation in this regard because it is equally possible to interpret the "coexisting organic disease" as also being related to the rejection by society which is implied in the act of commitment.

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In addition to these two points, there is another item of interest in the high rate of tuberculosis among migrants. Recent editorial comment on this subject[168] points out that 30 per cent of the tuberculosis occurring in immigrants to greater London occurs in the first year after immigration, during which time the individual is undoubtedly living in a more socially isolated situation than either before or after.

In 1954, Katz[167] pointed out that it is well known that tuberculosis is highest in the rooming house areas in and around the center of cities. In support of this notion that tuberculosis is common among persons living alone, McClure[169] found that men living in "flop houses" had several times the prevalence of active tuberculosis as would be expected of a group of men of equivalent age in the general population.

Finally, and perhaps most interesting of all, another study by Hawkins[170] indicates that the highest tuberculosis rate for Negroes is found among those who live in predominantly white districts, and the highest rate for whites is found among those who live in predominantly Negro districts.

It seems that such drastic alterations in the patterns of interpersonal relations as are caused by loss of a loved one, by sudden impoverishment, being sent to jail or a mental hospital, migration, and living in an area where one has few, if any, persons of one's own sort may be associated with clinical tuberculosis. One is, therefore, inclined to feel that the hypothesis of social isolation as a factor of interest in relation to tuberculosis is worthy of further study.

Data are not readily available to make a similar case for the accident prone; however, the information presented by Wolff[154] indicates that the accident-prone workers in a large manufacturing plant, in addition to being single and lacking an orderly family life, had a tendency to live in rooming houses. This again suggests an association with social isolation as for suicide and tuberculosis. A more systematic investigation of this topic is needed.

This discussion has been presented merely to illustrate the way in which data on the relationship between family structure and disease can be used. As a rule this kind of indirect information is not meaningful by itself. For example, it would be inappropriate to suggest that being the first born of a family is a "cause" for tuberculosis. However, it may well be appropriate to ask what characteristic of the first born contributes to tuberculosis, for we are always approaching causal relationships indirectly by establishing more and more meaningful associations. As time goes on, several statistically significant associations may acquire increased meaning by being grouped under one heading of a more general nature. In so doing, we move toward the scientific goal of describing the interrelationship of phenomena in the simplest possible terms. It, therefore, seems appropriate to conclude that the study of the relationship between family structure and disease will continue to be fruitful.

SUMMARY AND CONCLUSIONS

Parental deprivation seems to be associated with a number of psychiatric and psychosomatic diseases. The evidence is most striking for suicide, tuberculosis, and accidents. There is real need for a follow-up study of orphans, if such could be organized.

On the whole, the study of the relation of sibship size to health and disease has been difficult and to date relatively unproductive because of the multitude of interacting variables which must be taken into consideration in interpreting the results.

The eldest-to-youngest ratio (the ratio of the number of eldest children to number of youngest children in a sample) has proved to be a useful tool. Persons eminent in intellectual pursuits, people with asthma, and patients with tuberculosis tend towards high ratios, while persons with duodenal ulcer have low ratios.

It is now well-known that marital status has a marked relation to over-all mortality. This is most striking with respect to tuberculosis, suicide and other violent deaths, influenza and pneumonia, syphilis and its sequelae, and cirrhosis of the liver. With regard to morbidity, the association between rheumatoid arthritis and termination of marriage is notable particularly for men.

Methodologic problems have been discussed and some indications have been given of how data of this sort can contribute to new hypothesis.

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ERRATUM

In the October, 1960, issue of the JOURNAL, on page 403 of the editorial, "Of Misses and Medicine," the name of the second author should have been spelled Miriam Safren, M.A.

ANNOUNCEMENT

THE AMERICAN UROLOGICAL ASSOCIATION offers an annual award of $1,000 (first prize of $500, second prize $300, and third prize $200) for essays on the result of some clinical or laboratory research in Urology. Competition is limited to Urologists who have been graduated not more than 10 years and to hospital interns and residents doing research work in urology.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Hotel Biltmore, Los Angeles, Calif., May 22-25, 1961.

For full particulars write the Executive Secretary, William P. Didusch, 1120 North Charles St., Baltimore, Md. Essays must be in his hands before December 1, 1960.

REHABILITATION OF THE HOMEBOUND IN A SEMI-RURAL AREA
A Two-Year Experience With 120 Patients

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IMPROVED performance of everyday activities is often the major service which medicine offers the severely handicapped. This service can be provided in either the hospital or the home. The home setting offers some advantages. There the application of rehabilitation techniques is focused on the specific problems and resources of the patient's environment, rather than upon the standardized setting of a hospital rehabilitation ward. Rehabilitation in the home builds on the family's cooperation and relates the patient's treatment to the specific activities he used to perform and to the stimuli these offer for his participation in the rehabilitation process. Treated at home, the patient maintains his place in the family constellation whereas institutional rehabilitation, if prolonged, may require much effort by the entire rehabilitation team to reconstruct his place in his family.

Since World War II the trend toward shorter hospitalization has stimulated the development of home care programs for the chronically ill. Pioneered by Montefiore Hospital[1] in 1947, such programs have been largely centered in metropolitan hospitals. Of 19 home care programs recently reported in New York State, 18 were in New York City and only one was operated by a county health department.[2] These hospital-centered home care programs provide medical, nursing, social work, physical, occupational and speech therapy, housekeeping service, health education, hospital equipment and supplies, medications and medical supplies, orthopedic equipment, and transportation services.

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Thus defined, home care would seem a costly undertaking for suburban or semi-rural communities. Nevertheless, such communities have two basic health services—medical and nursing. It was suggested that an effective rehabilitation program might be grafted upon these two services with success and without immoderate expense.

THE PROJECT

To test this hypothesis the project described here was started in September, 1956, in northern Westchester County, New York State. This community has 60,000 residents in an area of 230 square miles. These agencies cooperated in the project: the District Nursing Association of Northern Westchester, Inc., the Westchester County Department of Health, and the New York State Chapter, Arthritis and Rheumatism Foundation. In the preceding four years the Chapter had developed home care services for arthritis patients in cooperation with two large urban visiting nurse agencies[3] while the District Nursing Association and the Health Department had recently pooled their nursing and other personnel.

To this staff the project added a physical therapist, full time, and a consultant physiatrist for half a day each month. The original plan of operation, previously described,[4] proved practical with minor modifications. Only the high points of the operation, therefore, will be noted here.

METHOD OF OPERATION

The corps of family physicians responsible for the medical supervision of the homebound patients constituted the project's basic community resource. The family doctor's approval was obtained in advance for every step of the rehabilitation process. The first cases were selected from among patients already receiving nursing care from the agency. Later, physicians in the community began referring patients for both rehabilitation and nursing, the agency's nurses began to suggest cases to the therapist, and patients' families began to ask for rehabilitation service.

With the doctor's approval, the physical therapist initiated the rehabilitation therapy, making his visits in company with the public health nurse.

TEACHING

Teaching occurred at the patient's bedside, in informal classes conducted by the physical therapist for the nurses, and in monthly case conferences.

The consultant physiatrist directed these conferences. He analyzed therapeutic procedures, guided the physical therapist and the public health nurses in their evaluation of progress and obstacles, and helped them to define rehabilitation goals, and to decide whether further progress might realistically be expected.

The special skills of all conference participants were drawn upon. For example, the Arthritis Foundation's Medical Director might comment on the clinical aspects of arthritis, the Director of the nursing agency on special nursing problems, the caseworker from the community family agency on the economic or social problems of the patient and his family, or the county nutritionist on reducing diets.

These regular discussions permitted the physiatrist to maintain a current assessment of the group's therapeutic effectiveness, to focus attention where needed, and to compare the rehabilitation potentials and problems encountered in different diagnostic groups. The psychiatrist did not treat patients.

THE ROLES OF NURSE AND THERAPIST

The first rehabilitation visits to the patient were made jointly by the therapist and nurse, after preliminary discussion of the patient's rehabilitation program. At the bedside, the physical therapist demonstrated exercises, identified functions in which the patient might improve and ways in which this could be accomplished, discussed self-help devices, and identified necessary environmental changes.

The therapist was responsible for all specialized therapeutic exercises such as those indicated for residual poliomyelitis, recent fractures, amputations, and cerebral palsy; he evaluated initial limitations of function and subsequent improvement or regression. Because of the special knowledge required, the therapist retained responsibility for gait analysis and training, as he did for muscle stretching, although in individual cases the therapist and nurse shared in giving the latter treatment.

The types of activity performed by the nurses included: teaching activities of daily living—washing, dressing etc.; teaching and giving simple exercises for maintenance and to prevent contractures; teaching the use of a paraffin dip for arthritic hands; use of pulleys; transfer from bed to chair or chair to standing; and proper bed positioning to prevent bed sores and contractures. At all times, the nurse might call on the therapist for help or counsel. The time required before any activity was turned over to the nurse by the therapist depended upon the individual nurse and how long it took to develop appropriate skill and confidence.

THE DATA

The following data were recorded for all cases: The patient's initial performance of eight functions: bed activities, chair activities, standing, walking, hygiene, dressing, eating, and homemaking. Performance was recorded as good, moderate, or poor-to-impossible, with a note indicating when the help of a device or of another person was needed. At intervals during the program, functional performance was re-evaluated. The closing evaluation was accompanied by a brief narrative summary. To ensure uniformity, function was assessed and the summaries were prepared by the physical therapist, in cooperation with the nurses.

Detailed activity of daily living analysis, it was felt, would include so many categories, each containing so few cases, as not to lend itself to significant analysis. Further, since we hoped to improve the day-by-day function of homebound patients, it seemed important to record functional restrictions in relatively broad categories, clearly related to the patients' home and family environment. This facilitated our teaching of the nurses, and helped obtain the patient's and his family's appreciation of the practical value of the goals toward which the patient's treatment was focused.

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THE PATIENTS

From September, 1956, through December, 1958, 144 patients entered this program, 120 receiving sufficient service to permit evaluation of results.

Diagnoses.—The 120 patients included 34 with cerebrovascular accidents, 33 with rheumatic disease, and 24 with fractures or amputations, while 29 had such diagnoses as poliomyelitis (6), multiple sclerosis (5), other neurological disorders (6), cardiovascular disease (4), senility (2), diabetes (2), and miscellaneous (4) (Table I).

In more than half of the records, one or more other disorders or symptoms were reported: obesity, hypertension, old fractures, diabetes, blindness, deafness, aphasia, history of peptic ulcers, Parkinsonism, and so forth.

Sex.—Three fifths of the group were females, as shown in Table I, the largest preponderance of women occurring among the rheumatic disease patients.

TABLE I. DIAGNOSIS AND SEX

DIAGNOSIS	MALE	FEMALE	TOTAL
Cerebrovascular accidents	12	22	34
Rheumatic diseases	5	28	33
Fractures or amputations	5	19	24
Miscellaneous	13	16	29
Total	35	85	120

Age.—The youngest patient was 5 and the eldest 93, as shown in Table II. The 7 patients under the age of 10 had fractures, poliomyelitis, or both. One of those over 90 years of age had generalized arteriosclerosis and the other osteoarthritis.

TABLE II. AGE OF PATIENTS, BY DIAGNOSIS

AGE (YRS.)	DIAGNOSIS				
	CEREBROVASCULAR ACCIDENTS	RHEUMATIC DISEASES	FRACTURES AMPUTATIONS	MISC.	TOTAL
5–19	0	1	3	7	11
20–39	0	4	0	3	7
40–59	6	7	4	8	25
60–79	23	17	10	8	58
80–93	5	4	7	3	19
Total	34	33	24	29	120

Table III indicates that the group's median age was 68, the patients with miscellaneous diagnoses being the youngest.

TABLE III. MEDIAN AGE

Cerebrovascular accidents	70
Rheumatic diseases	71
Fractures or amputations	69
Miscellaneous	52
Total group median	68

At the beginning all patients were significantly limited in the performance of one or more of the eight functional activities. Ninety-two patients had severe limitations; 28 patients were moderately limited.

Severe limitations of six, seven, or all eight functions were found in more than a third of the patients (Table IV), the cerebrovascular accident patients being most frequently subject to such severe, multiple limitations of function.

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TABLE IV. SEVERE LIMITATIONS OF SIX OR MORE FUNCTIONS

DIAGNOSIS	TOTAL PATIENTS	PATIENTS SEVERELY LIMITED IN 6 TO 8 FUNCTIONS	
		NO.	%
Cerebrovascular accidents	34	20	59
Rheumatic diseases	33	11	33
Fractures or amputations	24	3	12
Miscellaneous	29	13	45
Total	120	47	39

Treatment.—Over half of the patients required the program's services for less than 6 months; only a handful were followed for more than a year (Table V). In the course of treatment, the therapist and nurses made over 2,900 visits to the patients. The average number of visits per patient did not vary greatly among the four diagnostic groups.

TABLE V. DURATION OF TREATMENT AND NUMBER OF VISITS

DIAGNOSIS	DURATION OF TREATMENT				VISITS MADE	
	1–5 MO.	6–12 MO.	13 MO.	TOTAL	NO.	AVER. PER PATIENT
Cerebrovascular accidents	21	9	4	34	809	23
Rheumatic diseases	16	10	7	33	910	28
Fractures or amputations	16	7	1	24	507	21
Miscellaneous	17	7	5	29	696	24
Total	70	33	17	120	2,922	24

Aids to Function.—The great majority of the patients used aids to function—orthopedic equipment, self-help devices, and environmental adaptations (Table VI). The number of aids required by individual patients varied, the average being just under three per patient.

TABLE VI. NUMBER OF FUNCTIONAL AIDS, BY DIAGNOSTIC GROUP

DIAGNOSIS	NO. OF PATIENTS	NO. OF AIDS
Cerebrovascular accidents	32	102
Rheumatic diseases	28	80
Fractures or amputations	23	63
Miscellaneous	25	64
Total	108	309

As shown in Table VII, the aids used varied in character and complexity, from special eating utensils to a wheelchair with half a dozen attachments. About two thirds of the items were introduced by the project, the others being present at intake. In 21 cases, pre-existing items required alteration or adjustment to be fully usable.

TABLE VII. AIDS USED—TYPES AND SOURCES

	PRESENT AT INTAKE	INTRODUCED BY PROJECT	TOTAL
Canes	14	32	46
Wheelchairs	18	15	33
Walkers and walkerettes	12	19	31
Toilet and bath aids	5	22	27
Pulleys	4	21	25
Crutches	14	10	24
Bedropes, doorpulls, slings	2	22	24
Braces, prostheses, casts, pylons	16	5	21
Alterations and adjustments	0	21	21
Hospital beds, lifters, footboards	4	9	13
Rails, bars, grips and ramps	4	9	13
Eating and kitchen aids	0	8	8
Other*	6	17	23
Total	99	210	309

*Tilt boards, Seeing Eye Dogs, etc.

THE RESULTS

Some improvement in functional status was recorded for 80 patients when their cases were closed (Table VIII). Improvement was attained by almost all the patients with fractures and amputations and by over half of the 96 chronic disease patients. At the project's end, 83 patients performed normally in one or more functions, including 14 who performed normally in all eight.

TABLE VIII. FUNCTIONAL STATUS AT CLOSURE, BY DIAGNOSTIC GROUP

DIAGNOSIS	IMPROVED	UNIMPROVED	TOTAL
Cerebrovascular accidents	21	13	34
Rheumatic diseases	23	10	33
Fractures or amputations	23	1	24
Miscellaneous	13	16	29
Total	80	40	120

The extent of improvement is further defined in Table IX, which shows that the number of patients severely limited in six or more functions had been cut in half when the cases were closed, the cerebrovascular accident cases thus limited having been decreased by almost three quarters.

TABLE IX. PATIENTS WITH SEVERE LIMITATIONS IN 6 TO 8 FUNCTIONS

DIAGNOSIS	INTAKE	CLOSURE
Cerebrovascular accidents	20	6
Rheumatic diseases	11	5
Fractures or amputations	3	1
Miscellaneous	13	11
Total	47	23

The number of patients free of any severe functional limitation, as shown in Table X, doubled between intake and closure.

TABLE X. PATIENTS WITH NO SEVERE FUNCTIONAL LIMITATIONS

DIAGNOSIS	INTAKE	CLOSURE
Cerebrovascular accidents	5	13
Rheumatic diseases	10	17
Fractures or amputations	5	13
Miscellaneous	8	13
Total	28	56

In every function but eating at least three quarters of the patients were limited at intake, as shown in Table XI.

Improvements in standing and walking were achieved by over three fifths of the patients; over half improved in bed, chair, or personal hygiene activity; and at least a third improved in dressing, eating, and homemaking activity.

THE UNSUCCESSFUL CASES

One third of the patients did not improve. Functional performance remained unchanged in 25 patients, regressed in 6, and 9 patients died.

A NOTE ON COSTS

During the 28 months under review, the New York State Chapter, Arthritis and Rheumatism Foundation, contributed $13,850 to finance the physical therapist's salary, the consultant's expenses, and the purchase of equipment and devices, an outlay of $115 per patient. This excludes, of course, the regular professional and administrative expenses of the District Nursing Association.

DISCUSSION

This experiment provided rehabilitation services to suburban, homebound, chronic disease patients, most of whom improved in functional capacity. The project operated smoothly, and at modest cost. As the community and the patients seem generally representative of many suburban areas, some of the project's salient characteristics merit comment.

The project was operated through the voluntary visiting nurse agency with the cooperation of the county public health department and of the local physicians, the latter being ultimately responsible for the management of the patient. As the project grew, referrals by doctors for rehabilitation, as well as nursing care, increased.

The nurses learned such rehabilitation techniques as are appropriately performed by nursing personnel. They became increasingly capable of recognizing their patients' rehabilitation potential and of identifying environmental changes which might permit increased function. Responsibility for and direct participation in rehabilitation expanded the nurses' interest, heightened their morale, and enlarged the scope of their service.

The patient group was preponderantly female and of advanced age. It included four diagnostic categories of approximately equal size: cerebrovascular accidents, rheumatic diseases, fractures or amputations, and miscellaneous (largely neurological) disorders. Multiple diagnoses were present in half the cases. The group thus presented many typical geriatric characteristics.

The patients who had had cerebrovascular accidents included a relatively large number who initially were severely limited in most functions; this group achieved a greater reduction of such severe, multiple limitations than did most other patients.

Among the rheumatic disease patients, the number with severe and multiple functional limitations and the number who improved in function were about average for the whole group. Of the 10 patients with rheumatic disease who did not improve in function, 4 had problems deriving from low mentality or emotional difficulties appearing to require psychiatric or mental health clinic treatment.

Almost all of the fracture and amputation patients improved in function to some degree.

In addition to physical therapy modalities, physical aids to function, most of which were introduced by the project, were used by five sixths of the patients.

Because the project was an integral part of the local visiting nurse agency, the cooperation of other community services and other professional skills in the care of the patients was made more readily available.

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TABLE XI. CHANGE IN PERFORMANCE OF SPECIFIC FUNCTION

FUNCTION	PERFORMANCE	
	LIMITED AT INTAKE	IMPROVED AT CLOSURE
Walking	108	68
Hygiene	102	57
Dressing	99	48
Standing	97	61
Chair or wheelchair activities	91	50
Bed activities	90	47
Eating	61	27
Homemaking*	83	35

*Only 86 patients normally performed homemaking activities when well; the other 34 were children, men, or women with household help.

SUMMARY

By the addition of a physical therapist's services and monthly consultations with a physiatrist to the resources of an established visiting nurse agency, rehabilitation care was provided to 120 homebound, chronically ill patients in a semi-rural community in New York State during a 28 month period.

TABLE XII. THE UNSUCCESSFUL CASES

DIAGNOSIS	FUNCTION UNCHANGED	FUNCTION REGRESSED	DIED	TOTAL
Cerebrovascular accidents	8	0	5	13
Rheumatic diseases	7	2	1	10
Fractures or amputations	1	0	0	1
Miscellaneous	9	4	3	16
Total	25	6	9	40

Initially, all the patients were limited in performing one or more of eight major functions of everyday living. Upon conclusion, 80 patients had improved their performance of one or more of these eight functions; 25 remained unchanged in functional capacity; 6 had regressed, and 9 had died.

The simplicity of the project's operational structure and its moderate cost suggest the possibility of establishing similar services elsewhere.

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Book Reviews

TABULATING EQUIPMENT AND ARMY MEDICAL STATISTICS: Edited by Brig. Gen. Albert G. Love, U.S.A. (Ret.), Col. Eugene L. Hamilton, M.S.C., U.S.A.R., and Ida Levin Hellman, M.S.C. Office of the Surgeon General, Department of the Army, Washington, D. C. 1958 Pp. 189, indexed.

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The authors, on page 106 of this volume, cite a quotation attributed to Vegetius' *Art of War:* "An army raised without due regard to the choice of recruits, was never yet made a good army by any length of service". The truth of this adage is amply demonstrated by this volume, not only with regard to the problem of recruiting an army, but also in maintaining its health in war and peace. Much of the material presented in this volume has implications as well for civilian programs.

The authors set forth the evolution of the army medical statistics program and, as stated in the preface, "trace the development of medical records of the army in their individual service function, their compilation as medical statistics, and in their analysis leading to new knowledge. . . it is an excellent record of the evolution of medical statistics in effective use, rather than as statistics gathered for their own sake".

After an introductory chapter setting forth the establishment and development of the Medical Department of the Army, the second chapter traces the early development of medical records in the Army. It is pointed out that "when the United States secured its independence, . . ., no country in the world possessed trustworthy and detailed information concerning the health of its military and naval forces." But early in the 1800's "by the use of vital statistics. . . [Surgeon's General Lovell and Lawson] were able to stress the importance of their suggestions and *to point out of the improvement in the health of the Army that followed the approval of sanitary measures recommended by them*" (Italics reviewers).

Nevertheless, "When the Spanish American War began, there was no sick and wounded report from which vital statistics experience could be assembled rapidly and efficiently." How this experience was obtained is set forth in the next three chapters which deal with the development of the system of medical records and machine tabulating methods to deal with the huge job of summarizing, analyzing, and making available the tremendous volume of medical statistical intelligence present in the medical records. The chapter on the development of punch card equipment is a particularly fascinating one in view of the recent development of Univacs and their relatives. It is a tribute not only to Dr. Herman Hollerith, the inventor of the electrical tabulating equipment, but also to Dr. John Shaw Billings who "while engaged in the 10th census, that of 1880, (directed Dr. Hollerith's) attention to the need for some mechanical device for facilitating the compilation of population and similar statistics".

Chapters VI and VII deal with special and other statistical studies in World War I. These two chapters are among the most interesting in the book. They demonstrate that the medical statistical program of the Army has implications which extend beyond the military to throw light on problems of civil life as well. For example, the authors point out that the analysis of the selective service physical examinations had "important military bearing, since it indicated the proportion of men available for the different types of military service. It was important from the standpoint of the social and industrial life, since it would give some insight into the availability of the American population for the various occupations which the social organization required. It had social medical bearing, since it indicated the physical and mental status of the population in various sections of the country under the different sanitary conditions that prevailed and with the varying opportunities for medical and surgical treatment. In connection with this aspect of its important, it indicated the size and the nature of the task for those who would seek to improve,

by better conditions as well as by better care and surgical treatment, the physical and mental status of the population. Finally, it had biological and eugenic significance insofar as it might reveal the inherent failure of man to make a complete adaptation to the rapidly advancing requirements of a highly artificial civilization, and insofar as it might throw light on the constitutional limitations of the various races comprising the population to meet the conditions imposed by that civilization."

In addition to the analysis of the selective service examinations the authors describe a number of other studies which were carried out on World War I medical records and reports of physical examinations. Among these were:

1. an anthropometric description of men in the Army
2. a study of the relation of war casualties to hospital requirements
3. a long-range survey of the service efficiency and longevity of Army officers in relation to their health and physical measurements, both at the time of their admission to military service and during their service and
4. the preparation of standard tables of height, weight, and chest measurements.

Some of these studies are of considerable interest today. Thus the studies on hospital requirements have many of the earmarks of operations research and the biometric studies of army officers contain epidemiological observations of interest in regard to the problem of heart disease.

The remainder of the book deals with the changes instituted in the medical records, reporting and tabulating procedures since World War I and particularly with the adaptations necessary to deal with the enormous growth in the size of the Army during World War II and the complexities of a global war. The manner in which this was handled is in itself an exceedingly interesting story.

Today the Medical Statistics Division of the Surgeon General's Office considers its mission to be that of "providing the required statistical support for the Army's medical operations; to plan, devise, and operate a system of medical records and reports which will produce, at the right time and in the right amount, the quantitative facts needed to facilitate effective, continuous, current supervision of the world-wide medical service activities; and to provide a basis for realistic medium-and long-range plans for medical selection and separation of personnel, control of disease hazards and other environmental factors, provision of high-quality medical care to the sick and wounded, and efficient management of the hospitals and other medical resources of the Army."

The authors close with the hope that "those administering the Army will be as wise as the founding Fathers of the Medical Department and that there will be continued encouragement and support for the satisfactory compiling, analysis, and publication of both current and permanent statistics." The record of the medical statistical program through the years as set forth in this book amply justifies this hope.

Paul M. Densen

PLANNING HOMES FOR THE AGED. Edited by Geneva Mathiasen and Edward H. Noakes. New York, 1959, F. W. Dodge Corporation. Pp. 128, indexed. Price $12.75.

This is a collaborative volume which brings together the thinking of the people who create programs for and work with the aged as well as the architects who are responsible for designing the buildings where such programs will be carried out. It is a fine volume which will be very useful to those people planning physical facilities for the aged, for it covers almost every detail which needs to be kept in mind in their planning. It will also be of considerable use, I believe, to the architects, particularly since many more of these homes will be created during the next 10 years and often the architects will not have had any great personal experience with the needs of older people. This book contains a great many layouts of various kinds of homes presently in existence, along with critical comments about them and where they have failed.

The only reservation I have is based upon a philosophic difference. In every instance the homes are planned without any physical relationship to hospitals. Caring for older people means dealing with a good deal of illness and homes for the aged should have laboratory facilities, extensive infirmaries, diagnostic radiology, and such other necessary services. In one instance it is noted that many hospital people feel that homes for the aged should be on hospital grounds, but this thought is then dismissed with the observation that older people, because of their slower tempo, would be neglected in that the hospital's interest is elsewhere. While this is possible, of course,

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we all know that a home for the aged does not have to be on hospital grounds for the patients to be neglected—many, many homes are characterized by the virtual absence of a medical care program. I feel that homes for the aged could be built adjacent to hospitals quite profitably. If hospital philosophy becomes broad enough to make this possible, an appropriate share of the hospital's resources can be devoted to the older people so that they will not be deprived. I would liked to have seen architectural solutions to the problems of older people without duplication of medical care facilities which the hospital has in such abundance. There is little question that construction and maintenance costs would be less and much more could be provided for older people.

Despite the absence of a layout of such a home, this is a good book which will be most useful to people concerned with proper housing programs for the aged.

Martin Cherkasky

DRUGS OF CHOICE 1960-1961. Walter Modell, M.D., Editor. St. Louis 1960, The C. V. Mosby Company. Pp. 958, indexed. Price $13.50.

Dr. Modell's second edition of *Drugs of Choice* contains eleven new chapters that are not to be found in the first edition of this book. Such topics as "The physical and chemical considerations in the choice of drugs," "The choice of a local antiseptic," and "The choice of sedatives and tranquilizers in general medical practice," are worth-while additions, and will be of interest to many readers. The chapters dealing with disorders of metabolism, and eye, ear, nose, and throat disorders are of more limited interest.

It must be kept in mind that this is a collaborative textbook and contains the opinions of many authors, the majority of whom contributed to the first edition. In some cases there has been little added to this second book that was not already presented in the first one. However, the presentations are generally well organized and although many drugs that are no longer widely used are presented, the authors usually discriminate between these and their more effective counterparts. Furthermore, the emphasis on human pharmacology with references, whenever possible, to clinical experimentation makes this a more useful reference book for physicians than a standard textbook of pharmacology, such as that by Goodman and Gilman or by Drill and his collaborators.

On the negative side of the scale, the cost of the book is rather high, and when it is remembered that today's fact becomes tomorrow's fiction the wisdom of adding this volume to one's personal library is questionable. If Dr. Modell plans to publish more editions of this book on a yearly or bi-yearly basis, he might be better advised to issue supplements at more reasonable prices. The other objection concerns the amount of space devoted to the discussion, in most chapters, of clinical applications. Much of this information could have been excluded without great loss to the reader, and the happy result would have been a smaller, lighter, and cheaper book that could be read through in less time.

Nevertheless, this treatise contains much interesting and useful information and will be a good reference book—for a few years anyway.

John B. Murphy

A BIBLIOGRAPHY OF INTERNAL MEDICINE. SELECTED DISEASES. By Arthur L. Bloomfield, M.D. Chicago, 1960, U. of Chicago Press. Pp. 312, Indexed. Price $6.00.

Professor Bloomfield has us once again in his debt. This follow-up volume to his work on communicable diseases is if anything more interesting than the first book. The style is the same: a delightful annotated bibliography, the references more or less in chronologic order, and emphasizing the contributions of the pioneer observers. The table of contents starts with auricular fibrillation and ends with trichinosis. Although the focus is on cardiovascular and metabolic diseases, there are also sprightly articles on chlorosis, leukemia, asthma, and Hodgkin's disease. If there is any fault in the book, it lies in the problem of how to handle the more recent literature; Dr. Bloomfield's task is obviously easier and more pleasant when he has to deal with the giants of the past than with the less impressive or less clear contributions of our own time.

This is a book for every medical student and doctor, to say nothing of the jaded roundsmaker who is looking for a way to instill new life into his bedside discussions.

Louis Lasagna

TREATMENT OF CANCER IN CLINICAL PRACTICE. Peter B. Kunkler and Anthony J. H. Rains, Editors. The Williams & Wilkins Company, Baltimore, exclusive U. S. agents. Price $19.00.

It is difficult, if not impossible, for an individual physician or surgeon to understand and apply the increasing body of knowledge relevant to the treatment of patients with neoplastic diseases. The therapeutic specialization which stems from the biologic diversity of the diseases involved and the more highly refined technical skills employed does not in itself confer better treatment. This text, therefore, is designed to present a balanced view of the various therapeutic procedures pertinent to the treatment of cancer and the reasoned arguments on which they are based It is directed mainly at the graduate student.

To accomplish their objective, the editors have assembled contributions from several eminent British surgeons and radiotherapists. The preliminary chapters present the principles of patient management and the surgical, radiotherapeutic, and chemotherapeutic approach to their illnesses. Subsequent sections are devoted to a brief description of a therapeutic plan applicable to various malignancies according to their anatomic sites of origin and the extent of their spread.

It is difficult for the reviewer to appraise critically such a text, particularly since current therapy remains hampered by a fundamental ignorance of the disease processes involved and in practice is based on philosophy as much as on science. However, it seems that the suggested approaches to commonly encountered clinical problems would meet with general approval. A definite attempt has been made to outline the basis for each therapeutic choice and each chapter includes a number of pertinent references. It is also fair to say that some experienced therapists would object to sections of the text, based in part on their personal technical competence and clinical experience.

The material is presented in a clear and easily understood manner and is appropriately illustrated. Students and practitioners alike should find this volume a welcome supplement to the standard medical texts, which devote their attentions chiefly to the clinical manifestations and diagnosis of the neoplastic diseases.

Albert H. Owens, Jr.

THE LIFESPAN OF ANIMALS. Ciba Foundation Colloquis on Ageing, Volume 5. Edited by G. E. W. Wolstenholme, O.B.E., M. A., M.B., B.Ch., and Maeve O'Connor, B.A. Boston, 1959, Little, Brown and Co. Pp. 324, indexed. Cumulative index to Vols. 1-5. Price $9.50.

That individual animals, including man, continually mature and then inevitably senesce, is one of the basic fascinations of life. Senescence has been a recognized part of our culture as long as records have been kept. However, scientific study of the phenomenon of ageing has been given renewed emphasis in recent years. In keeping with their aim of bringing together different disciplines to discuss a fundamental question, the Ciba Foundation organized 5 years ago a series of colloquia on ageing. The present volume is the last of five, all of which have been excellent. In this colloquium statisticians, demographers, pathologists, biologists, genetecists, entomologists, and cell physiologists join together to give a uniquely critical review of the question, "Just how long do animals live and what keeps them alive until their appointed time arrives?"

It is clear that the answer is not yet in. A mixture of Gompertz functions, entropy, bronchiectasis, and nephrosis in rats, differential mortality in male and female houseflies, survivorship curves in ungulates in zoos, stud books of English thoroughbred racing horses, and longevity of fishes in aquaria still produces a bewildering reaction. What is normal senescence and what is disease? Is there one basic factor involved in ageing, or are there many? Has there been any change in the life span of man in the last hundred years?

The function of these symposia is not to give final answers, but to clear away confusion of thought and data. Anyone who proposes to study ageing, either as a biologist or as a geriatrician, will need to refer to these volumes, and particularly to this last one. Here he will find such a clear description of so many of the facets of this basic problem, that he cannot but be stimulated to inquire further and to think more clearly.

Frederick B. Bang

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CURRENT VIRUS RESEARCH. *British Medical Bulletin*, Volume 15, No. 3. September 1959. Pp. 260, not indexed. Price $3.25. (Published by the Medical Department, The British Council, 65 Davies Street, London, W 1.

Progress in scientific areas frequently occurs in irregular surges; during such periods considerable gaps may develop between the development of information its and effective dissemination to and utilization by others in biology and medicine. In the past decade, advances have been made in our understanding of viruses, their interaction with cells, and the diseases they produce. In several instances, the importance of this information has had immediate importance in therapeutics. The development of in vitro technique for growing poliomyelitis virus in cell cultures made possible the development of an effective formalin-inactivated vaccine. Similarly, the development of plaque-assay techniques for animal viruses has enabled investigators to isolate virus mutants and has facilitated the development of live attenuated poliovirus vaccine strains, currently under clinical evaluation.

These contributions in the realm of improved techniques have been fundamental. Other equally important developments are still in the domain of the laboratory worker. The findings of Isaacs and his colleagues that the virus-infected cell produces a substance, termed interferon, capable of protecting other cells from virus infection, has excited wide interest among workers in the field.

It is fortunate then that these and other recent advances have been recounted in clear, precise, informative articles in the British Medical Bulletin. The authors, many of whom are leaders in their fields, have neatly succeeded in bridging the informational gap and have produced articles of value both to the active worker in the field and to physicians and scientists working in other areas. The articles cover many topics from genetics to the newly isolated respiratory agents; gathered together under one cover, they provide a concise summary of recent developments in virology.

Allan H. Levy

PUBLIC ASSISTANCE MEDICAL CARE: AREAS OF NEEDED RESEARCH AND AN ANNOTATED BIBLIOGRAPHY. By S. J. Axelrod, M.D., Chicago, 1959, American Public Welfare Association, 1313 East 60th Street. Pp. 63, not indexed. Price $2.00.

This is the first report from the Medical Assistance Research Project sponsored by the American Public Welfare Association and conducted by Doctor S. J. Axelrod and his associates at the Bureau of Public Health Economics, University of Michigan. The report consists of outline of needed research in public assistance medical care and an annotated bibliography.

It appears at a timely moment when sizeable Federal-state programs for medical care of public assistance recipients have been in operation for two or three years. Considerable attention is now being focused on the quality of the medical care in these programs and what is being accomplished by them.

The outline, Areas of Needed Research, gives a broad view of the many important questions that should be answered if the hundreds of millions of dollars now being devoted to public assistance medical care are to be utilized with greatest effectiveness. It is heartening that the Bureau of Medical Economics proposes to develop specifications for minimum basic data to be collected by state public assistance medical programs, for evaluation of the medical programs. The importance of such an endeavor can be seen in the success of the National Institute of Mental Health during the past few years in standardizing data regarding state mental hospital services. Good record keeping constitutes one of the best ways of getting at the quality of medical care and it is to be hoped that this new effort will succeed.

Following the statement on needed research, there is a carefully selected and well arranged annotated bibliography concerning research on public assistance medical care that has already been completed. Administrators of public assistance medical care programs and others concerned will find this bibliography a valuable guide to literature on the subject which is based upon factual data. So much opinion on this subject is formed on the basis of impression and prejudice that it is indeed useful to have this compilation of actual research in the field. Of some interest is the extent to which public assistance medical care has attracted the research endeavors of Federal and State

Public Health Departments, as well as the efforts of Universities. This reflects the increasing recognition of the importance of public assistance medical care as a contributor to public health.

The report represents a scholarly approach, in the tradition of the Bureau of Medical Economics of the University of Michigan.

Lester Breslow

BIOCHEMISTRY OF HUMAN GENETICS. Ciba Foundation Symposium, Jointly with the International Union of Biological Sciences. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P., and Cecilia M. O'Connor, B.Sc. Boston: Little, Brown and Co., 1959. Pp. 349, indexed. Price $9.50.

The astonishing advances which have occurred in human biochemical genetics during the past decade are the subject of this symposium. As an authentic summary of these advances, presented in most part by those principally responisble, this book is a great advance in itself. In nearly every topic the individual essays can serve as introductions to the uniformed and at once provide new information to concerned investigators not present. The discussion periods, which admirably proceed to profitable speculation, are alone worth the price of purchase. The speed with which the book has followed the conference, held in Naples during May of 1959, sustains the usefulness of the individual contributions.

If the reader of this review has not already called his bookseller he can perhaps be persuaded by a partial list of topics and participants. These include: Hereditary Galactosemia by Kalckar; Serum Cholinesterase Types by Kalow; The Genetics of Primaquine Sensitivity by Childs and Zinkham; "Hybridization" of the Hemoglobin Molecule by Itano, Singer, and Robinson; The Protein Structure of Abnormal Human Hemoglobins by Hunt and Ingram; Foetal Myoglobin by Rossi-Fanelli and colleagues; Plasma Protein Variants by H. Harris, Robson, and Siniscalco; Haptoglobins and Transferrins by Smithies and Connell; Three sections on the blood group substances, by Morgan, by Watkins, and by Ceppellini; Inherited Human Gamma Globulins by Grubb. Joshua Lederberg, S. Brenner, Macfarlane Burnet, Lionel Penrose, James Neel, G. Pontecorvo, and H. Eagle are some of those who figure prominently in discussion.

Samuel H. Boyer

HENRY E. SIGERIST ON THE SOCIOLOGY OF MEDICINE. Edited by Milton I. Roemer, M.D. Foreword by James M. Mackintosh, M.D. New York, 1960, M.D. Publications, Inc. Pp. 397, indexed. Price $6.75.

This second collection of Sigerist essays is less rewarding than the first, primarily because of the limited scope imposed on the editor by the title of the book. Sigerist was an ardent champion of socialized medicine, and an admirer of Russian health measures, and his reflections are worth reading—but not over and over. There is a sameness to the essays that reflects less on their author—since he wrote them for different audiences—than on the anthologist who has pulled them together into one book. The result is a volume which will be of significant interest to Sigerist fans, of some interest to medical historians, but of little interest to most doctors.

Louis Lasagna

MEDIEVAL AND RENAISSANCE MEDICINE. By Benjamin Lee Gordon, M.D., F.I.C.S. New York, 1959, Philosophical Library. Pp. 843, indexed.

Within the covers of this large new book Doctor Gordon has collected an amazing amount of material from hundreds of sources, both well known and obscure. The most useful function of the volume will be to serve as a reference and source book, although there is also a fair amount of direct quotation from writings generally only abstracted or summarized in historical texts, for which at least some readers will be grateful. Unfortunately, the author lacks the sure narrative touch of a Garrison, Sigerist, or Castiglioni, and the result is a choppy, repetitious, badly edited book which is less fun to read than it should have been.

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